U.S. DEPARTMENT OF COMMERCE
Patent and Trademark Office

# SEARCH REQUEST FORM

OCT -4 2001

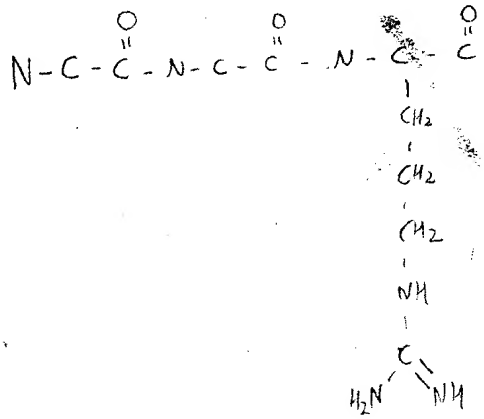
Requestor's Name: Jeffrey E. Russel

Serial Number: 09/053,872

Date: 10-4-2001 Phone: 308-3975 Art Unit: 1653
CM1-9801 / CM1-9807

**Search Topic:**
Please write a detailed statement of search topic. Describe specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples or relevant citations, authors keywords, etc., if known. For sequences, please attach a copy of the sequence. You may include a copy of the broadest and/or most relevant claim(s).

Please search the following partial structure:



FIXai

keywords are Factor IX, Factor IXa, thrombosis, clot, anticoagulant.

Thank you.

JER

## STAFF USE ONLY

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Total time:
Number of Searches:
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**Type of Search**
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_____ A.A. Sequence
_____ Structure
_____ Bibliographic

**Vendors**
_____ IG Suite
_____ STN
_____ Dialog
_____ APS
_____ Geninfo
_____ SDC
_____ DARC/Questel
_____ Other

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FILE LAST UPDATED: 5 Oct 2001  (20011005/ED)

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information and abstracts were added for over 2.2 million references
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L1              STR
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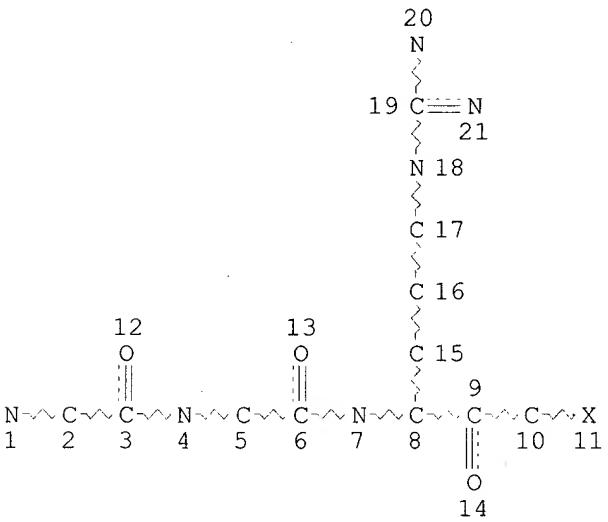


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NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  21
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STEREO ATTRIBUTES: NONE
L3          239 SEA FILE=REGISTRY SSS FUL L1
L4          644 SEA FILE=REGISTRY ABB=ON  PLU=ON  FACTOR(L)(IX? OR 1X?) OR
                THROMBOSIS OR CLOT? OR ANTICOAGULANT? OR ANTI(W)COAGULANT?
L5          124 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L3
L6       257934 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L4 OR ?FACTOR?(5A)(IX? OR
                1X?) OR ?THROMBOS? OR ?CLOT? OR ?COAGULA?
L7           51 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L5 AND L6


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L7   ANSWER 1 OF 51  HCAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2001:397075  HCAPLUS
DOCUMENT NUMBER:          135:30730
TITLE:                    Novel detection method for a functionally active form
                          of an enzyme in biological samples and a kit using an
                          immobilized enzyme inhibitor or a mutant
INVENTOR(S):              Lawrence, Daniel A.; Day, Duane
PATENT ASSIGNEE(S):       American Red Cross, USA
SOURCE:                   PCT Int. Appl., 70 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
     ---------------   ----  --------       ---------------   --------
     WO 2001038560      A2   20010531       WO 2000-US32315   20001122
         W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN,
             CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR,
             HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT,
             LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU,
             SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN,
             YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY,
             DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF,
             BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.:                    US 1999-167553   A1 19991122
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AB The present method utilizes the capture of the functionally active form of an enzyme that covalently binds or binds with a dissocn. const. of 1 x 10-9M or less to an enzyme inhibitor or mutant. The present invention is directed to a method for detecting a functionally active form of an enzyme in a biol. sample, comprising contacting an enzyme inhibitor or mutant immobilized on a solid substrate with the biol. sample, and measuring the binding of the enzyme inhibitor or mutant to the active form of the enzyme by a detectable label, wherein the enzyme inhibitor specifically forms a covalent bond or binds with a dissocn. const. of 1 x 10-9M or less with the active form of the enzyme. Further, the present invention is directed to an anal. element useful for carrying out the detection of a functionally active form of an enzyme in biol. sample, that includes an enzyme inhibitor or mutant immobilized on a solid substrate, wherein the enzyme inhibitor specifically binds or binds with a dissocn. const. of 1 x 10-9M or less to the active form the enzyme. This anal. element is

included in a kit with an anal. reagent conjugated to a detectable label or conjugated to a reactive mol. that generates a detectable label, wherein the reagent specifically binds to the active form of the enzyme that binds to the enzyme inhibitor. Specific enzyme inhibitors or mutants are designed to covalently bind to specific clin. important enzymes. These enzyme inhibitors contain modifications that facilitate binding to a solid support and optionally modifications that affect the binding to a target enzyme or affect the stability of the inhibitor. The method is particularly useful in measuring the presence of enzymes, such as tPA, elastase, cathepsin G and prostate specific antigen. Also disclosed is a method of immobilizing enzyme inhibitors or mutants on a solid substrate yet retaining the property of covalently binding or binding with a dissocn. const. of 1 x 10-9M or less to a functionally active enzyme.

IT **9001-92-7**, Proteinase
RL: ANT (Analyte); ANST (Analytical study)
(detection method for functionally active form of enzyme in biol. samples and kit using immobilized enzyme inhibitor or mutant)

IT **91386-14-0 130690-46-9**
RL: ARG (Analytical reagent use); ANST (Analytical study); USES (Uses)
(enzyme inhibitor; detection method for functionally active form of enzyme in biol. samples and kit using immobilized enzyme inhibitor or mutant)

L7 ANSWER 2 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:262619 HCAPLUS
DOCUMENT NUMBER: 135:17638
TITLE: The role of tissue factor/factor VIIa in the pathophysiology of acute thrombotic formation
AUTHOR(S): Girard, Thomas J.; Nicholson, Nancy S.
CORPORATE SOURCE: Pharmacia Corporation, Creve Coeur, MO, 63167, USA
SOURCE: Curr. Opin. Pharmacol. (2001), 1(2), 159-163
CODEN: COPUBK; ISSN: 1471-4892
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review, with 40 refs. Tissue factor (TF) is the essential cofactor for the **coagulation** protease factor VIIa (FVIIa), initiating the **coagulation** cascade. The role of TF in thrombotic diseases is becoming increasingly evident. Recent findings suggest that inhibition of TF/FVIIa activity could be important in the prevention of clin. sequelae assocd. with plaque rupture or vessel damage that exposes TF to blood. Furthermore, selective inhibitors of TF/FVIIa may be assocd. with less bleeding risk than other antithrombotic agents. Several TF/FVIIa inhibitors are in development, including the protein-based inhibitors (such as NAPc2, Corsevin M, FFR-FVIIa, and Tifacogin). Research into the development of small mol. inhibitors is on-going, but is at a less advanced stage.

IT **74392-49-7D**, reaction products with factor VIIa
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(tissue factor/factor VIIa role in pathophysiol. of acute thrombotic formation in human)

REFERENCE COUNT: 40
REFERENCE(S):
(3) Badimon, J; Circulation 1999, V99, P1780 HCAPLUS
(4) Carson, S; Blood Coagl Fibrinolysis 1996, V7, P303 HCAPLUS
(6) Courtman, D; Circ Res 1998, V82, P996 HCAPLUS
(9) Dennis, M; Nature 2000, V404, P465 HCAPLUS
(11) Giesen, P; Proc Natl Acad Sci USA 1999, V96,

P2311 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 3 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:228928 HCAPLUS
DOCUMENT NUMBER: 134:247248
TITLE: Bivalent inhibitor of FVIIa/tissue factor/FXa complex and therapeutic use
INVENTOR(S): Freskgaard, Per-Ola; Jakobsen, Palle
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001021661 | A1 | 20010329 | WO 2000-DK516 | 20000919 |

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: DK 1999-1333 A 19990920
US 1999-159773 P 19991015

AB A bivalent serine protease inhibitor of **coagulation** factor VIIa and factor Xa is provided which comprises: (i) a first serine protease inhibitor binding to factor VIIa; (ii) a linker moiety; and (iii) a second serine protease inhibitor binding to factor Xa. Also provided are a method for inhibiting the two different serine proteases factor VIIa and factor Xa simultaneously and selectively when the two serine proteases becomes localized on the membrane protein tissue factor (TF). The compds. and method are useful for prevention or treatment of FVIIa/TF-related diseases or disorders, e.g. deep venous **thrombosis**, arterial **thrombosis**, post surgical **thrombosis**, coronary artery bypass graft (CABG), percutaneous transdermal coronary angioplasty (PTCA), stroke, tumor metastasis, inflammation, septic chock, hypotension, ARDS, pulmonary embolism, disseminated intravascular **coagulation** (DIC), vascular restenosis, platelet deposition, myocardial infarction, angiogenesis, or the prophylactic treatment of mammals with atherosclerotic vessels at risk for **thrombosis**. Prepn. of e.g. octanedioic acid bis-[(1-(1-(1-chloroacetyl-4-guanidinobutylcarbamoyl)2-phenylethylcarbamoyl)2-phenylethyl)amide] is described.

IT **331664-31-4DP**, complexes with factor VIIa
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(bivalent inhibitor of FVIIa/tissue factor/FXa complex and therapeutic use)

IT **331664-31-4P 331664-32-5P 331664-33-6P 331664-34-7P**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(bivalent inhibitor of FVIIa/tissue factor/FXa complex and therapeutic use)

IT **74392-51-1**
RL: RCT (Reactant)
(reaction; bivalent inhibitor of FVIIa/tissue factor/FXa complex and therapeutic use)

REFERENCE COUNT: 3
REFERENCE(S): (1) George, J; US 5106833 A 1992 HCAPLUS
(2) John, M; US 5242810 A 1993 HCAPLUS
(3) The Board Of Trustees Of The Leland Stanford Junior University; WO 9961055 A1 1999 HCAPLUS

L7 ANSWER 4 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2001:63783 HCAPLUS
DOCUMENT NUMBER: 134:125963
TITLE: Use of FVIIa or a tissue factor antagonist for regulating gene expression and cell migration or chemotaxis
INVENTOR(S): Ezban, Mirella; Petersen, Lars Christian; Siegbahn, Agneta
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.
SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2001005353 | A2 | 20010125 | WO 2000-DK401 | 20000714 |
| WO 2001005353 | A3 | 20010719 | | |
| W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 2000058075 | A5 | 20010205 | AU 2000-58075 | 20000714 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| DK 1999-1023 | A | 19990714 |
| US 1999-148300 | P | 19990811 |
| DK 1999-1117 | A | 19990812 |
| WO 2000-DK401 | W | 20000714 |

AB The present invention relates to use of VII, FVIIa, tissue factor (TF) agonist, modified/inactivated FVII (FVIIai), and/or another TF antagonist in therapeutic treatment of pathol. conditions that can be related to cell migration or treated by specific regulation of cell migration or chemotaxis. The invention also relates to the use of these compds. in therapeutic treatment of pathol. conditions that can be related to regulation of expression of at least one gene in a cell, e.g., Cyr61 gene. For example, Cyr61 expression was increased in time-dependent manner in quiescent fibroblasts treated with 5 .mu.g/mL VIIa. The expression was peaked at about 45 min and thereafter declined to the base level in 2-3 h. Since it had been reported that expression of Cyr61 in mouse fibroblasts after stimulation with serum and growth factor was sustained for several hours (up to 8-10 h) before repression occurs, the effect of serum and

PDGF on kinetics of Cyr61 expression in quiescent human fibroblasts, WI-38 was examd. Cyr61 is expressed only transiently upon 29 stimulation with PDGF and become fully repressed 2 h after the addn. of stimuli. Similar results were obtained with serum-induced expression of Cyr61 (data not shown). Treatment of fibroblasts with as low as 0.1 .mu.g/mL FVIIa was sufficient to induce the expression of Cyr61 and a plasma concn. of FVII(a) (0.5 .mu.g/mL, 10 nM) resulted in a prominent response, close to the maximal.

IT **9001-25-6P**, Blood **coagulation** factor VII
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(use of FVII(a) or tissue factor antagonist for regulating gene expression and cell migration or chemotaxis)

IT **9001-25-6D**, Blood-**coagulation** factor VII, reaction products with peptide derivs. **74392-49-7D**, reaction products with factor VII **74392-51-1D**, reaction products with factor VII **200802-98-8D**, reaction products with factor VII **321680-09-5D**, reaction products with factor VII
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(use of FVII(a) or tissue factor antagonist for regulating gene expression and cell migration or chemotaxis)

L7 ANSWER 5 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:190947 HCAPLUS
DOCUMENT NUMBER: 132:231982
TITLE: Ihibitors of factor Xa activity for fibroblast inhibition
INVENTOR(S): Blanc-Brude, Olivier; Laurent, Geoffrey J.
PATENT ASSIGNEE(S): University College London, UK
SOURCE: PCT Int. Appl., 47 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 2000015250 | A2 | 20000323 | WO 1999-GB3092 | 19990913 |
| WO 2000015250 | A3 | 20000720 | | |
| W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9958778 | A1 | 20000403 | AU 1999-58778 | 19990913 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| GB 1998-19921 | A | 19980911 |
| GB 1999-8838 | A | 19990416 |
| WO 1999-GB3092 | W | 19990913 |

AB The use of an inhibitor of factor Xa activity in the prodn. of a medicament for the prevention or treatment of organ damage assocd. with factor Xa stimulation of fibroblasts resulting in the proliferation of fibroblasts and/or the prodn. of procollagen by fibroblasts is described.

Blocking the proliferation of fibroblasts and/or the procollagen promoter activity of fibroblasts reduces the prodn. of collagen by these cells. Hence, the deposition of extracellular matrix, which would otherwise disturb the organization of the tissue and result in the loss of function of the organ, can be diminished. All inhibitors of factor Xa and derivs. thereof known to the skilled person fall within the scope of the invention, such as tick **anticoagulant** peptide, antistasin, GGACK, and DX 9065.

IT **65113-67-9 129737-17-3**, Tick **anticoagulant** peptide
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibitor of factor Xa activity for prevention or treatment of organ damage assocd. with fibroblast proliferation and prodn. of procollagen)

L7 ANSWER 6 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:779112 HCAPLUS
DOCUMENT NUMBER: 132:18788
TITLE: Modified factor VII for **anticoagulant** therapy
INVENTOR(S): Hart, Charles E.; Petersen, Lars C.; Hedner, Ulla; Rasmussen, Mirella E.
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.; ZymoGenetics, Inc.
SOURCE: U.S., 34 pp., Cont.-in-part of U.S. 5,833,982.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5997864 | A | 19991207 | US 1997-871003 | 19970606 |
| US 5788965 | A | 19980804 | US 1995-475845 | 19950607 |
| US 5833982 | A | 19981110 | US 1996-660289 | 19960607 |
| US 6183743 | B1 | 20010206 | US 1999-378907 | 19990820 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1995-475845 | A2 | 19950607 |
| US 1996-660289 | A2 | 19960607 |
| US 1991-662920 | B2 | 19910228 |
| WO 1992-US1636 | A2 | 19920228 |
| US 1993-65725 | B2 | 19930521 |
| WO 1994-US5779 | A2 | 19940523 |
| US 1994-327690 | A2 | 19941024 |
| US 1997-871003 | A3 | 19970606 |

AB The catalytic active site of Factor VII is modified to produce a compd. which effectively interrupts the blood **coagulation** cascade. The modifications render Factor VIIa substantially unable to activate plasma **Factors** X or **IX**. The invention relates to novel methods of treatment and uses of modified Factor VII for preventing or treating myocardial injury assocd. with post-ischemic reperfusion, for improving regional myocardial blood flow during reperfusion, and maintaining or improving vascular patency in a patient, as well as topical application of modified Factor VII at vascular sites susceptible to thrombus formation.

IT **9001-28-9**, Blood **Coagulation factor ix**
**9001-29-0**, **Coagulation** factor x
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); BIOL (Biological study); PROC (Process)
(activation of; modified **factor** VII for **anticoagulant** therapy)

IT **9001-25-6**, Blood-**coagulation** factor VII
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified factor VII for **anticoagulant** therapy)
IT **69024-84-6 74392-51-1 200802-98-8**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified factor VII for **anticoagulant** therapy)
REFERENCE COUNT: 43
REFERENCE(S): (1) Anon; WO 92/15686 1929 HCAPLUS
(2) Anon; WO 86/06408 1986 HCAPLUS
(3) Anon; EP 255771 1988 HCAPLUS
(5) Anon; WO 90/03390 1990 HCAPLUS
(6) Anon; WO 90/15619 1990 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 7 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:640718 HCAPLUS
DOCUMENT NUMBER: 131:267054
TITLE: Methods using a **factor IXa** compound for treating an ischemic disorder and improving stroke outcome
INVENTOR(S): Pinsky, David J.; Stern, David; Schmidt, Ann Marie; Rose, Eric; Solomon, Robert A.
PATENT ASSIGNEE(S): The Trustees of Columbia University In the City of New York, USA
SOURCE: PCT Int. Appl., 174 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9949880 | A1 | 19991007 | WO 1999-US7175 | 19990401 |
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| RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG | | | | |
| AU 9934621 | A1 | 19991018 | AU 1999-34621 | 19990401 |
| EP 1067953 | A1 | 20010117 | EP 1999-916266 | 19990401 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |

PRIORITY APPLN. INFO.: US 1998-53871 A2 19980401
WO 1999-US7175 W 19990401

AB A method is provided for treating an ischemic disorder in a subject which comprises administering to the subject a pharmaceutically acceptable **factor IXa** compd. in a sufficient amt. over a sufficient period to treat the ischemic disorder. The invention further provides a method for treating an ischemic disorder in a subject which comprises administering to the subject a pharmaceutically acceptable form of inactivated **Factor IXa** in a sufficient amt. over a sufficient period of time to inhibit **coagulation** so as to treat

the ischemic disorder.

IT **37316-87-3**, Blood **coagulation factor IXa**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**factor IXa** compd. for treating ischemic disorder and improving stroke outcome)

IT **69024-84-6**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(**factor IXa** compd. for treating ischemic disorder and improving stroke outcome)

REFERENCE COUNT: 1
REFERENCE(S): (1) Moller; CA 2141642 A1 1995 HCAPLUS

L7 ANSWER 8 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:77868 HCAPLUS
DOCUMENT NUMBER: 131:2413
TITLE: Evaluation of the thrombin inhibitor D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone (PPACK) with the factor Xa inhibitor 1,5-dansyl-L-glutamyl-L-glycyl-L-arginine chloromethylketone (GGACK) as **anticoagulants** for critical care clinical chemistry specimens
AUTHOR(S): Lyon, Martha E.; Drobot, Duane W.; Rutledge Harding, Sheila; Lyon, Andrew W.
CORPORATE SOURCE: College of Medicine, Departments of Pharmacologyand Pathology, University of Saskatchewan, Saskatoon, SK, Can.
SOURCE: Clin. Chim. Acta (1999), 280(1-2), 91-99
CODEN: CCATAR; ISSN: 0009-8981
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The objective of this study was to det. whether a thrombin inhibitor (PPACK) and a factor Xa inhibitor (GGACK) either alone or in combination can **anticoagulate** whole blood without biasing the anal. of several crit. care analytes. Whole blood **clot** time was used to assess **anticoagulant** efficacy. The anal. biases mediated by the **anticoagulants** on glucose, urea, creatinine, electrolytes, amylase, lactate dehydrogenase, creatine kinase, ionized calcium and pH were assessed. The protease inhibitor mixt. (100 .mu.mmol/l PPACK+500 .mu.mol/l GGACK) was more a potent **anticoagulant** than the individual agents at the same concns. Both PPACK and GGACK, alone and in combination, reduced the activity of creatine kinase and amylase by 3-10% while the remaining crit. care analytes were less affected. In conclusion, PPACK and GGACK mixts. can effectively **anticoagulate** whole blood, but the mixts. exert pre-anal. influences that limit the anal. versatility of these novel plasma-matrixes.

IT **69024-84-6**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(evaluation of the thrombin inhibitor D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone with the factor Xa inhibitor dansyl-L-glutamylglycyl-L-arginine chloromethylketone as **anticoagulants**)

REFERENCE COUNT: 27
REFERENCE(S): (2) Ciuti, R; Clin Chem 1989, V35, P1562 HCAPLUS
(3) Claeson, G; Blood Coagul and Fibrino 1994, V5, P411 HCAPLUS

(5) Fareed, J; Medical Clinics of North Am 1994, V78, P713 HCAPLUS
(6) Fenton, J; Blood Coagul Fibrino 1991, V2, P69 HCAPLUS
(7) Hauptmann, J; Blood Coagul Fibrino 1993, V4, P577 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 9 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:56363 HCAPLUS
DOCUMENT NUMBER: 130:119600
TITLE: Modified Factor VII for treatment of blood **coagulation**-related disorders
INVENTOR(S): Berkner, Kathleen L.; Petersen, Lars Christian; Hart, Charles E.
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.; Zymogenetics, Inc.
SOURCE: U.S., 18 pp., Cont.-in-part of U.S. Ser. No. 65,725, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5861374 | A | 19990119 | US 1996-537807 | 19960212 |
| WO 9427631 | A1 | 19941208 | WO 1994-US5779 | 19940523 |

W: AU, CA, HU, JP, US
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

PRIORITY APPLN. INFO.: US 1991-662920 B2 19910228
US 1993-65725 B2 19930521
WO 1994-US5779 W 19940523

AB The catalytic active site of Factor VII is modified to produce a compd. which effectively interrupts the blood **coagulation** cascade. The modification renders Factor VIIa substantially unable to activate plasma **Factors** X or **IX**. Pharmaceutical compns. of the modified Factor VII are used to treat a variety of **coagulation**-related disorders.

IT **9001-28-9**, **Factor ix 9001-29-0**,
Factor x
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(activation of, inhibition of; modified **Factor** VII for treatment of blood **coagulation**-related disorders)

IT **9001-25-6**, Blood-**coagulation** factor VII
**69024-84-6**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified Factor VII for treatment of blood **coagulation**-related disorders)

REFERENCE COUNT: 23
REFERENCE(S): (1) Anon; WO 86/06408 1986 HCAPLUS
(2) Anon; EP 255771 1988 HCAPLUS
(3) Anon; WO 89/09612 1989 HCAPLUS
(4) Anon; WO 90/03390 1990 HCAPLUS
(5) Anon; WO 90/15619 1990 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 10 OF 51 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:731783 HCAPLUS
DOCUMENT NUMBER: 130:7391
TITLE: Modified factor VII for interruption of the blood **coagulation** cascade
INVENTOR(S): Berkner, Kathleen L.; Petersen, Lars Christian; Hart, Charles E.; Hedner, Ulla; Bregengaard, Claus
PATENT ASSIGNEE(S): Zymogenetics Inc., USA; Novo Nordisk A/S
SOURCE: U.S., 28 pp., Cont.-in-part of U.S. Ser. No. 475,845. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5833982 | A | 19981110 | US 1996-660289 | 19960607 |
| US 5817788 | A | 19981006 | US 1994-327690 | 19941024 |
| US 5788965 | A | 19980804 | US 1995-475845 | 19950607 |
| WO 9747651 | A1 | 19971218 | WO 1997-DK251 | 19970606 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9730906 | A1 | 19980107 | AU 1997-30906 | 19970606 |
| AU 735012 | B2 | 20010628 | | |
| EP 910580 | A1 | 19990428 | EP 1997-925917 | 19970606 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| CN 1221427 | A | 19990630 | CN 1997-195294 | 19970606 |
| US 5997864 | A | 19991207 | US 1997-871003 | 19970606 |
| BR 9709661 | A | 20000425 | BR 1997-9661 | 19970606 |
| JP 2000513720 | T2 | 20001017 | JP 1998-501082 | 19970606 |
| US 6168789 | B1 | 20010102 | US 1998-189607 | 19981110 |
| NO 9805668 | A | 19990204 | NO 1998-5668 | 19981204 |
| US 6183743 | B1 | 20010206 | US 1999-378907 | 19990820 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1991-662920 | B2 | 19910228 |
| US 1993-65725 | B2 | 19930521 |
| US 1994-327690 | A2 | 19941024 |
| US 1995-475845 | A2 | 19950607 |
| WO 1992-US1636 | A2 | 19920228 |
| WO 1994-US5779 | A2 | 19940523 |
| US 1996-660289 | A | 19960607 |
| US 1997-871003 | A3 | 19970606 |
| WO 1997-DK251 | W | 19970606 |

AB The catalytic active site of Factor VII is modified to produce a compd. which effectively interrupts the blood **coagulation** cascade. The modifications render Factor VIIa substantially unable to activate plasma **Factors** X or **IX**. Pharmaceutical compns. of the modified Factor VII are used to treat a variety of **coagulation**-related disorders, including platelet deposition, vascular **thrombosis**, ischemic reperfusion, acute closure of a coronary artery, vascular restenosis secondary to balloon angioplasty, endarterectomy, reductive atherectomy, stent placement, laser therapy or rotablation.

IT **9001-28-9**, Blood **coagulation factor ix**

**9001-29-0**, Blood **coagulation** factor x
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(activation of; modified **factor** VII for interruption of the blood **coagulation** cascade)

IT **69024-84-6 74392-51-1 200802-98-8**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(modified factor VII for interruption of the blood **coagulation** cascade)

IT **9001-25-6P**, Blood **coagulation** factor vii
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modified factor VII for interruption of the blood **coagulation** cascade)

REFERENCE COUNT: 35
REFERENCE(S):
(1) Anon; WO 9215686 1929 HCAPLUS
(2) Anon; WO 8606408 1986 HCAPLUS
(3) Anon; EP 255771 1988 HCAPLUS
(5) Anon; WO 9003390 1990 HCAPLUS
(6) Anon; WO 9015619 1990 HCAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:527047 HCAPLUS
DOCUMENT NUMBER: 129:156938
TITLE: Modified Factor VII for treatment of **coagulation**-related disorders
INVENTOR(S): Berkner, Kathleen L.; Petersen, Lars Christian; Hart, Charles E.; Hedner, Ulla; Bregengaard, Claus
PATENT ASSIGNEE(S): Novo Nordisk A/s, Den.; Zymogenetics, Inc.
SOURCE: U.S., 26 pp. Cont.-in-part of U.S. Ser. No. 327,690.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5788965 | A | 19980804 | US 1995-475845 | 19950607 |
| US 5817788 | A | 19981006 | US 1994-327690 | 19941024 |
| BR 9509135 | A | 19951103 | BR 1995-9135 | 19951024 |
| CA 2203280 | AA | 19960502 | CA 1995-2203280 | 19951024 |
| WO 9612800 | A1 | 19960502 | WO 1995-US13925 | 19951024 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| AU 9540142 | A1 | 19960515 | AU 1995-40142 | 19951024 |
| EP 789759 | A1 | 19970820 | EP 1995-938944 | 19951024 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 11500408 | T2 | 19990112 | JP 1995-514147 | 19951024 |
| HU 78098 | A2 | 19991028 | HU 1997-2221 | 19951024 |
| US 5833982 | A | 19981110 | US 1996-660289 | 19960607 |
| NO 9701878 | A | 19970623 | NO 1997-1878 | 19970423 |
| US 5997864 | A | 19991207 | US 1997-871003 | 19970606 |

| | | | | |
|---|---|---|---|---|
| US 6168789 | B1 | 20010102 | US 1998-189607 | 19981110 |
| US 6183743 | B1 | 20010206 | US 1999-378907 | 19990820 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1991-662920 | B2 | 19910228 |
| US 1993-65725 | B2 | 19930521 |
| US 1994-327690 | A2 | 19941024 |
| WO 1992-US1636 | A2 | 19920228 |
| WO 1994-US5779 | A2 | 19940523 |
| US 1995-475845 | A | 19950607 |
| WO 1995-US13925 | W | 19951024 |
| US 1996-660289 | A2 | 19960607 |
| US 1997-871003 | A3 | 19970606 |

AB The catalytic active site of Factor VII is modified to produce a compd. which effectively interrupts the blood **coagulation** cascade. The modifications render Factor VIIa substantially unable to activate plasma **Factors** X or **IX**. Pharmaceutical compns. of the modified Factor VII are used to treat a variety of **coagulation**-related disorders including those assocd. with angioplasty.

IT **9001-28-9**, Blood **coagulation factor ix**
**9001-29-0**, Blood **coagulation** factor x
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(activation of, inhibition of; modified **Factor** VII for treatment of **coagulation**-related disorders)

IT **9001-25-6P**, Blood **coagulation** factor vii
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BPR (Biological process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(modified Factor VII for treatment of **coagulation**-related disorders)

IT **69024-84-6 74392-51-1 200802-98-8**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified Factor VII for treatment of **coagulation**-related disorders)

L7 ANSWER 12 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:208429 HCAPLUS
DOCUMENT NUMBER: 128:266260
TITLE: Methods using selectin antagonists, carbon monoxide, and inactivated **factor IX** for treating an ischemic disorder and improving stroke outcome
INVENTOR(S): Pinsky, David J.; Stern, David; Schmidt, Ann Marie; Rose, Eric A.; Connoly, E. Sander; Solomon, Robert A.; Prestigiacomo, Charles J.
PATENT ASSIGNEE(S): Trustees of Columbia University In the City of New York, USA; Pinsky, David J.; Stern, David; Schmidt, Ann Marie; Rose, Eric A.; Connoly, E. Sander; Solomon, Robert A.; Prestigiacomo, Charles J.
SOURCE: PCT Int. Appl., 230 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9813058 | A1 | 19980402 | WO 1997-US17229 | 19970925 |

W: AU, CA, JP, MX, US
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE

| | | | | |
|---|---|---|---|---|
| AU 9745942 | A1 | 19980417 | AU 1997-45942 | 19970925 |
| EP 951292 | A1 | 19991027 | EP 1997-944453 | 19970925 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI | | | | |
| JP 2001501612 | T2 | 20010206 | JP 1998-515905 | 19970925 |
| PRIORITY APPLN. INFO.: | | | US 1996-721447 A2 | 19960927 |
| | | | WO 1997-US17229 W | 19970925 |

AB A method for treating an ischemic disorder in a subject comprises administering to the subject a pharmaceutically acceptable form of a selectin antagonist in a sufficient amt. over a sufficient time to prevent white blood cell accumulation. Also provided is a method for treating an ischemic disorder in a subject which comprises administering to the subject carbon monoxide gas in a sufficient amt. over a sufficient time. Further provided is a method for treating an ischemic disorder in a subject which comprises administering to the subject a pharmaceutically acceptable form of inactivated **Factor IX** in a sufficient amt. over a sufficient time to inhibit **coagulation.**

IT **9001-28-9P**, Blood **coagulation factor IX**
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inactivated; selectin antagonists, carbon monoxide, and inactivated **factor IX** for treating an ischemic disorder and improving stroke outcome)

IT **37316-87-3**, Blood **coagulation factor IXa 69024-84-6**
RL: RCT (Reactant)
(reaction, in **factor IXai** prepn.; selectin antagonists, carbon monoxide, and inactivated **factor IX** for treating an ischemic disorder and improving stroke outcome)

L7 ANSWER 13 OF 51 HCAPLUS COPYRIGHT 2001 ACS

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|---|---|
| ACCESSION NUMBER: | 1998:24935 HCAPLUS |
| DOCUMENT NUMBER: | 128:136311 |
| TITLE: | Antithrombotic efficacy of inactivated active site recombinant factor VIIa is shear dependent in human blood |
| AUTHOR(S): | Orvim, Una; Barstad, R. Marius; Orning, Lars; Petersen, Lizette B.; Ezban, Mirella; Hedner, Ulla; Sakariassen, Kjell S. |
| CORPORATE SOURCE: | Nycomed Imaging AS, Oslo, N-0371, Norway |
| SOURCE: | Arterioscler., Thromb., Vasc. Biol. (1997), 17(11), 3049-3056<br>CODEN: ATVBFA; ISSN: 1079-5642 |
| PUBLISHER: | American Heart Association |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |

AB Several studies have indicated a profound role for factor VII(a) [FVII(a)] in venous and arterial thrombogenesis. In the present study, we quantified the inhibitory efficacy of dansyl-glutamyl-glycyl-arginyl-recombinant FVIIa (DEGR-rFVIIa) on acute thrombus formation. Thrombus formation was elicited by immobilized tissue factor (TF) in a parallel-plate perfusion chamber device at blood flow conditions characterized by wall shear rates of 100 S-1 (veins) and 650 S-1 (medium-sized healthy arteries). Native human blood was drawn directly

from an antecubital vein by a pump into a heparin-coated mixing device in which DEGR-rFVIIa (0.09 to 880 nmol/L final plasma concn.) or buffer was mixed homogeneously with flowing blood. Subsequently, the blood was passed over a plastic coverslip coated with TF and phospholipids in the parallel-plate perfusion chamber. Fibrin deposition, platelet-fibrin adhesion, and platelet thrombus vol. triggered by this surface were measured by morphometry. DEGR-rFVIIa inhibited thrombus formation in a dose-dependent manner, but the efficacy was shear rate dependent. At a wall shear rate of 100 S-1, the IC50 (50% inhibition) was 30 nmol/L, whereas at 650 S-1, the IC50 was 0.6 nmol/L. Binding studies to immobilized TF under flow conditions using surface plasmon resonance revealed a significantly higher on-rate for DEGR-rVIIa and FVIIa than for FVII, 2.8.times.105, 2.6.times.105, and 1.8.times.105 M-1 S-1, resp. This indicates that a contributing factor to the shear-dependent efficacy may be a differential importance of on-rates at arterial and venous blood flow conditions.

IT **69024-84-6D**, reaction products with recombinant factor VIIa
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antithrombotic efficacy of inactivated active site recombinant factor VIIa is shear dependent in human blood)

L7 ANSWER 14 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1998:15776 HCAPLUS
DOCUMENT NUMBER: 128:97711
TITLE: Active site-modified blood-**coagulation** factor VIIa and its activity as an **anticoagulant**
INVENTOR(S): Petersen, Lars Christian; Hart, Charles E.; Hedner, Ulla; Rasmussen, Mirella Ezban
PATENT ASSIGNEE(S): Novo Nordisk A/S, Den.; Zymogenetics
SOURCE: PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9747651 | A1 | 19971218 | WO 1997-DK251 | 19970606 |
| W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM | | | | |
| RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5833982 | A | 19981110 | US 1996-660289 | 19960607 |
| AU 9730906 | A1 | 19980107 | AU 1997-30906 | 19970606 |
| AU 735012 | B2 | 20010628 | | |
| EP 910580 | A1 | 19990428 | EP 1997-925917 | 19970606 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO | | | | |
| BR 9709661 | A | 20000425 | BR 1997-9661 | 19970606 |
| JP 2000513720 | T2 | 20001017 | JP 1998-501082 | 19970606 |
| NO 9805668 | A | 19990204 | NO 1998-5668 | 19981204 |

PRIORITY APPLN. INFO.: US 1996-660289 A 19960607

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|---|---|---|
| US | 1991-662920 | B2 19910228 |
| US | 1993-65725 | B2 19930521 |
| US | 1994-327690 | A2 19941024 |
| US | 1995-475845 | A2 19950607 |
| WO | 1997-DK251 | W 19970606 |

AB The catalytic active site of Factor VII is modified to produce a compd. which effectively interrupts the blood **coagulation** cascade. The modifications comprise site-specific mutagenesis of the active site serine-344 to an alanine residue, or chem. modification of the active site with serine proteinase inhibitors such as peptide halomethyl ketones (e.g., dansyl-Glu-Gly-Arg-chloromethyl ketone [DEGRck] or Phe-Phe-Arg-chloromethyl ketone). The modifications render Factor VIIa still able to bind to cell-surface tissue factor, but substantially unable to activate plasma **Factors** X or **IX**. Thus, DEGR-factor VIIa has not enzymic activity, yet it binds to tissue factor and acts as a competitive antagonist for wild-type factor VIIa, thereby inhibiting the subsequent steps in the extrinsic pathway of **coagulation** leading to the generation of thrombin. The invention relates to novel methods of treatment and uses of modified Factor VII for treating preventing or treating myocardial injury assocd. with post-ischemic reperfusion, for improving regional myocardial blood flow during reperfusion, and maintaining or improving vascular patency in a patient, as well as topical application of modified Factor VII at vascular sites susceptible to thrombus formation.

IT **69024-84-6D**, reaction product with factor VIIa **74392-51-1D** , reaction product with factor VIIa **200802-98-8D**, reaction product with factor VIIa
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(active site-modified blood-**coagulation** factor VIIa and its activity as an **anticoagulant**)

L7 ANSWER 15 OF 51 HCAPLUS COPYRIGHT 2001 ACS

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|---|---|
| ACCESSION NUMBER: | 1997:723758 HCAPLUS |
| DOCUMENT NUMBER: | 128:112217 |
| TITLE: | Identification of potential activators of proteinase-activated receptor-2 |
| AUTHOR(S): | Fox, Mark T.; Harriott, Patrick; Walker, Brian; Stone, Stuart R. |
| CORPORATE SOURCE: | Department of Haematology, University of Cambridge, MRC Centre, Cambridge, UK |
| SOURCE: | FEBS Lett. (1997), 417(3), 267-269<br>CODEN: FEBLAL; ISSN: 0014-5793 |
| PUBLISHER: | Elsevier |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |

AB In order to identify physiol. activators of proteinase-activated receptor-2 (PAR-2), a peptide chloromethane inhibitor (biotinyl-Ser-Lys-Gly-Arg-CH2Cl) based on the cleavage site for activation of PAR-2 was synthesized and tested with 12 trypsin-like serine proteinases. The second-order rate const. (ki/Ki) for the formation of the covalent proteinase-inhibitor complex varied by 2 .times. 105-fold between the proteinases. Biotinyl-Ser-Lys-Gly-Arg-CH2Cl reacted very rapidly with trypsin, acrosin from sperm and tryptase from mast cells: the ki/Ki values with these proteinases were greater than 105 M-1 s-1. Thus, the specificity of these proteinases matched the sequence of the activation site of PAR-2 and it can be concluded that these proteinases are potential physiol. activators of PAR-2.

IT **201746-19-2**

RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(identification of potential activators of proteinase-activated receptor-2 by inhibition with a receptor-based peptide)

L7 ANSWER 16 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1997:671086 HCAPLUS
DOCUMENT NUMBER: 127:355191
TITLE: The effect of active site-inhibited factor VIIa on tissue factor-initiated **coagulation** using platelets before and after aspirin administration
AUTHOR(S): Kjalke, Marianne; Oliver, Julie A.; Monroe, Dougald M.; Hoffman, Maureane; Ezban, Mirella; Hedner, Ulla; Roberts, Harold R.
CORPORATE SOURCE: Center Thrombosis Hemostasis, Univ. North Carolina, Chapel Hill, NC, USA
SOURCE: Thromb. Haemostasis (1997), 78(4), 1202-1208
CODEN: THHADQ; ISSN: 0340-6245
PUBLISHER: Schattauer
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Active site-inactivated factor VIIa has potential as an antithrombotic agent. The effects of D-Phe-L-Phe-L-Arg-chloromethyl ketone-treated factor VIIa (FFR-FVIIa) were evaluated in a cell-based system mimicking in vivo initiation of **coagulation**. FFR-FVIIa inhibited platelet activation (as measured by expression of P-selectin) and subsequent large-scale thrombin generation in a dose-dependent manner with IC50 values of 1.4 nM and 0.9 nM, resp. Kd for factor VIIa binding to monocytes and Ki for FFR-FVIIa competing with factor VIIa were similar (11.4 pM and 10.6 pM, resp.), showing that FFR-FVIIa binds to tissue factor in the tenase complex with the same affinity as factor VIIa. Using platelets before and after ingestion of aspirin (1.3 g), there were no differences in the IC50 values of FFR-FVIIa after aspirin ingestion, the IC50 values were 1.7 nM for P-selectin expression, and 1.4 nM for thrombin generation. This shows that aspirin treatment of platelets does not influence the inhibition of tissue factor-initiated **coagulation** by FFR-FVIIa, probably because thrombin activation of platelets is not entirely dependent upon expression of thromboxane A2.
IT **9001-28-9, Factor IX 9001-29-0,** Factor X **74392-49-7D**, reaction products with factor VIIa
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(active site-inhibited **factor** VIIa effect on tissue factor-initiated **coagulation** using platelets before and after aspirin administration)

L7 ANSWER 17 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:391879 HCAPLUS
DOCUMENT NUMBER: 125:49317
TITLE: Inhibition of blood **coagulation** with modified factor VII
INVENTOR(S): Berkner, Kathleen L.; Petersen, Lars Christian; Hart, Charles E.; Hedner, Ulla; Bregengaard, Claus
PATENT ASSIGNEE(S): Zymogenetics, Inc., USA; Novo Nordisk A/s
SOURCE: PCT Int. Appl., 68 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9

PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9612800 | A1 | 19960502 | WO 1995-US13925 | 19951024 |
| W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA, UZ, VN | | | | |
| RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG | | | | |
| US 5817788 | A | 19981006 | US 1994-327690 | 19941024 |
| US 5788965 | A | 19980804 | US 1995-475845 | 19950607 |
| BR 9509135 | A | 19951103 | BR 1995-9135 | 19951024 |
| AU 9540142 | A1 | 19960515 | AU 1995-40142 | 19951024 |
| EP 789759 | A1 | 19970820 | EP 1995-938944 | 19951024 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| JP 11500408 | T2 | 19990112 | JP 1995-514147 | 19951024 |
| NO 9701878 | A | 19970623 | NO 1997-1878 | 19970423 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1994-327690 | A | 19941024 |
| US 1995-475845 | A | 19950607 |
| US 1991-662920 | B2 | 19910228 |
| US 1993-65725 | B2 | 19930521 |
| WO 1995-US13925 | W | 19951024 |

AB A method for inhibiting blood **coagulation** comprises administering to a patient a Factor VII modified at its catalytic center such that its ability to activate **Factors** X or **IX** is inhibited. The modified Factor VII may be prepd. by reaction with a serine protease inhibitor such as a peptide halomethyl ketone, or by culture of transgenic cells. A gene encoding [Ala-344]Factor VII was prepd. and expressed in BHK 570 cells. In a **clotting** assay mixt. contg. Factor VII-deficient plasma and thromboplastin, addn. of this Factor VII analog had no effect on **clotting** time. The analog was shown to compete with unaltered Factor VII for tissue factor. Pharmaceutical compns. of the modified Factor VII are used to treat a variety of **coagulation**-related disorders.

IT **9001-25-6DP**, Blood-**coagulation** factor VII, modified
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibition of blood **coagulation** with modified factor VII)

IT **69024-84-6DP**, reaction product with blood-**coagulation** factor VII
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibition of blood **coagulation** with modified factor VII)

IT **9001-28-9**, Blood-**coagulation factor IX**
**9001-29-0**, Blood-**coagulation** factor X
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition of blood **coagulation** with modified factor VII)

L7 ANSWER 18 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:807055 HCAPLUS
DOCUMENT NUMBER: 123:305972
TITLE: Inhibition of thrombin by arginine-containing peptide chloromethyl ketones and bis chloromethyl ketone-albumin conjugates
AUTHOR(S): Odake, Shinjiro; Kam, Chih-Min; Powers, James C.

CORPORATE SOURCE: School Chemistry Biochemistry, Georgia Institute Technology, Atlanta, GA, 30332-0400, USA
SOURCE: J. Enzyme Inhib. (1995), 9(1), 17-27
CODEN: ENINEG; ISSN: 8755-5093
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Arg-contg. peptide chloromethyl ketones including D-Phe-Pro-Arg-CH2Cl derivs. have been synthesized and tested as inhibitors for thrombin and several blood **coagulation** enzymes. The parent compd., D-Phe-Pro-Arg-CH2Cl is still the best thrombin inhibitor in the series with kobs/[I] value of 107 M-1s-1. Extension by one amino acid (Phe or Gly), or a peptide moiety (ClCH2-Arg<-Pro<-D-Phe<-CO-CO-, ClCH2-Arg<-Pro<-D-Phe<-CO-(CH2)3-CO-, where < - indicates a reversed amino acid residue, -CO-CHR-NH-) on the N-terminus of D-Phe-Pro-Arg-CH2Cl reduces the inhibition const. by 1-2 orders of magnitude, which indicates the importance of a free amino group at the N-terminus. The tripeptide D-Phe-Pro-Arg-CH2Cl and related tetrapeptide inhibitors inhibit thrombin more potently than **factor IXa** and plasma kallikrein by 2-5 orders of magnitude. Z-Arg-CH2Cl and Phe-Phe-Arg-CH2Cl which contain a largely hydrophobic group at the P2 site inhibit thrombin poorly. All the peptide chloromethyl ketones inhibit plasma kallikrein moderately with kobs/[I] values of 102-103 M-1s-1 but inhibit **factor IXa** poorly (kobs/[I] < 20 M-1s-1). Conjugates of albumin with the bis chloromethyl ketones [(CO-D-Phe-Pro-Arg-CH2Cl)2, (CH2)3-(CO-D-Phe-Pro-Arg-CH2Cl)2] were prepd. and are potent thrombin inhibitors. These conjugates are model compds. for developing specific thrombus-bound thrombin inhibitors which may have therapeutic application in the treatment of **coagulation** disorders.

IT **169871-13-0P**
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(inhibition of thrombin by arginine-contg. peptide chloromethyl ketones and bis chloromethyl ketone-albumin conjugates)

IT **169388-20-9P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(inhibition of thrombin by arginine-contg. peptide chloromethyl ketones and bis chloromethyl ketone-albumin conjugates)

L7 ANSWER 19 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1995:761808 HCAPLUS
DOCUMENT NUMBER: 123:164691
TITLE: Blood **coagulation** retardants and devices
INVENTOR(S): Lyon, Martha E.; Henderson, Paul; Malik, Sohail; Kenny, Margaret A.; Lyon, Andrew W.
PATENT ASSIGNEE(S): University of Washington, USA
SOURCE: PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9514788 | A1 | 19950601 | WO 1994-US13537 | 19941123 |

W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SI, SK, TJ, TT, UA,

UZ, VN
RW: KE, MW, SD, SZ, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG

| | | | | |
|---|---|---|---|---|
| AU 9511862 | A1 | 19950613 | AU 1995-11862 | 19941123 |
| PRIORITY APPLN. INFO.: | | | US 1993-157880 | 19931124 |
| | | | WO 1994-US13537 | 19941123 |

AB The invention provides methods of using **anticoagulants** to retard the **coagulation** of blood, so that properties and functions of blood, plasma, and blood cells may be detd. anal. The methods do not interfere with electrochem. techniques use to detect divalent cations and permit accurate anal. of many analytes within a single blood sample, which currently require sep. **anticoagulated** blood samples. The serine protease inhibitors used may be combined with each other or blood cell activation, aggregation, and adhesion inhibitors in mixts. that provide **anticoagulant** activity. The methods permit, for the first time, the possibility of using a single blood sample to perform a full range of blood, plasma, and blood cell analyses. The **anticoagulation** effect of D-phenylalanyl-prolyl-arginyl chloromethyl ketone is detd.

IT **69024-84-6**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(blood **coagulation** retardants and devices)

L7 ANSWER 20 OF 51 HCAPLUS COPYRIGHT 2001 ACS

| | |
|---|---|
| ACCESSION NUMBER: | 1995:341015 HCAPLUS |
| DOCUMENT NUMBER: | 122:142487 |
| TITLE: | Modified blood **coagulation** factor VII for treatment of **coagulation**-related disorders |
| INVENTOR(S): | Berkner, Kathleen L.; Petersen, Lars Christian; Hart, Charles E. |
| PATENT ASSIGNEE(S): | Zymogenetics, Inc., USA; Novo Nordisk A/S |
| SOURCE: | PCT Int. Appl., 49 pp.<br>CODEN: PIXXD2 |
| DOCUMENT TYPE: | Patent |
| LANGUAGE: | English |
| FAMILY ACC. NUM. COUNT: | 9 |
| PATENT INFORMATION: | |

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9427631 | A1 | 19941208 | WO 1994-US5779 | 19940523 |
| W: AU, CA, HU, JP, US | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| CA 2162726 | AA | 19941208 | CA 1994-2162726 | 19940523 |
| AU 9469560 | A1 | 19941220 | AU 1994-69560 | 19940523 |
| AU 703110 | B2 | 19990318 | | |
| EP 699075 | A1 | 19960306 | EP 1994-918092 | 19940523 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE | | | | |
| HU 73329 | A2 | 19960729 | HU 1995-3312 | 19940523 |
| HU 219682 | B | 20010628 | | |
| JP 08510746 | T2 | 19961112 | JP 1994-500869 | 19940523 |
| US 6039944 | A | 20000321 | US 1995-464233 | 19950605 |
| US 5861374 | A | 19990119 | US 1996-537807 | 19960212 |
| US 6168789 | B1 | 20010102 | US 1998-189607 | 19981110 |
| US 6183743 | B1 | 20010206 | US 1999-378907 | 19990820 |
| PRIORITY APPLN. INFO.: | | | US 1993-65725 A | 19930521 |
| | | | US 1991-662920 B3 | 19910228 |
| | | | WO 1992-US1636 A2 | 19920228 |

WO 1994-US5779 W 19940523
US 1994-327690 A3 19941024
US 1995-475845 A2 19950607
US 1996-660289 A3 19960607
US 1997-871003 A3 19970606

AB The catalytic active site of Factor VII is modified to produce a compd. which effectively interrupts the blood **coagulation** cascade. The modification Ser344.fwdarw.Ala renders Factor VIIa substantially unable to activate plasma **Factors** X or **IX**. The catalytic site modification by also be effected by reaction of factor VII with a protease inhibitors such as an organophosphorus compd., a sulfanyl fluoride, a peptide halomethyl ketone, or an azapeptide. Pharmaceutical compns. of the modified Factor VII are used to treat a variety of **coagulation** -related disorders [no data].

IT **9001-25-6P**, Blood **coagulation** factor VII
RL: BAC (Biological activity or effector, except adverse); BMF (Bioindustrial manufacture); BPN (Biosynthetic preparation); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(modified human blood **coagulation** factor VII for treatment of **coagulation**-related disorders)

IT **9001-28-9**, Blood **coagulation factor IX**
**9001-29-0**, Blood **coagulation** factor X
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(modified human blood **coagulation factor** VII for treatment of **coagulation**-related disorders)

IT **69024-84-6**
RL: RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(modified human blood **coagulation** factor VII for treatment of **coagulation**-related disorders)

L7 ANSWER 21 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1994:430502 HCAPLUS
DOCUMENT NUMBER: 121:30502
TITLE: Method and kit for measuring heparin using limiting amount of Factor Xa or thrombin
INVENTOR(S): Nesheim, Michael E.; Manuel, Reginald P.
PATENT ASSIGNEE(S): Research Corp. Technol., Inc., USA
SOURCE: U.S., 9 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 5308755 | A | 19940503 | US 1992-895078 | 19920608 |
| WO 9512817 | A1 | 19950511 | WO 1993-CA452 | 19931105 |
| W: CA, JP | | | | |
| RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE | | | | |
| EP 727047 | A1 | 19960821 | EP 1993-923990 | 19931105 |
| EP 727047 | B1 | 19980826 | | |
| R: AT, BE, CH, DE, DK, ES, FR, GB, IE, IT, LI, NL, SE | | | | |
| AT 170291 | E | 19980915 | AT 1993-923990 | 19931105 |

PRIORITY APPLN. INFO.:
US 1992-895078 19920608
EP 1993-923990 19931105
WO 1993-CA452 19931105

AB A method for assaying body fluid samples contg. heparin and a diagnostic kit are described. Since the reactions go to completion, timing of the assay is not required. The sample is mixed with a heparin-dependent protease inhibitor and either a heparin-independent irreversible inhibitor or a protease substrate. The **coagulation** enzyme (protease) is then added in a limiting quantity and it either distributes between the heparin-dependent inhibitor and the heparin-independent irreversible inhibitor, or the heparin-dependent inhibitor and the protease substrate. The distribution pattern of complex formation of the protease with the two inhibitors or the level of product of the protease-catalyzed hydrolysis of the substrate are used as measures of the heparin activity. The irreversible inhibitor is a peptidyl chloromethyl ketone and the substrate is a synthetic chromogenic or fluorogenic compd. that produces a readily measured signal. Heparin was assayed against Factor Xa with chromogenic substrate S2222, antithrombin III, and a limiting quantity of Factor Xa.

IT **155735-17-4**
RL: ANST (Analytical study)
(in heparin detn. by assay using limiting amt. of Factor Xa or thrombin)

L7 ANSWER 22 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:641086 HCAPLUS
DOCUMENT NUMBER: 119:241086
TITLE: The structure of a designed peptidomimetic inhibitor complex of .alpha.-thrombin
AUTHOR(S): Wu, Tswei Ping; Yee, Vivien; Tulinksy, A.; Chrusciel, R. Alan; Nakanishi, Hiroshi; Shen, Richard; Priebe, Cheryl; Kahn, Michael
CORPORATE SOURCE: Dep. Chem., Michigan State Univ., East Lansing, MI, 48824, USA
SOURCE: Protein Eng. (1993), 6(5), 471-8
CODEN: PRENE9; ISSN: 0269-2139
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Thrombin displays remarkable specificity, effecting the removal of fibrinopeptides A and B fibrinogen through the selective cleavage of two Arg-Gly bonds between the 181 Arg/Lys-Xaa bonds in fibrinogen. Significant advances have been made in recent years towards understanding the origin of the specificity of cleavage of the Arg16-Gly17 bond of the A.alpha.-chain of human fibrinogen. The authors have previously proposed a model for the bound structure of fibrinopeptide A7-16 (FPA), based upon NMR data, computer-assisted mol. modeling and the synthesis and study of peptidomimetic substrates and inhibitors of thrombin. The authors now report the structure of the ternary complex of an FPA mimetic (FPAM), hirugen and thrombin at 2.5 .ANG. resoln. (R-factor = 0.138) and specificity data for the inhibition of thrombin and related trypsin-like proteinases by FPAM. The crystallog. structures of FPA and its chloromethyl ketone deriv. bound to thrombin were detd. Although there are differences between these structures in the above modeled FPA structure and that of the crystal structure of FPAM bound to thrombin, the .phi.,.psi. angles in the crit. region of P1-P2-P3 in all of the structures are similar to those of bovine pancreatic trypsin inhibitor (BPTI) in the BPTI-trypsin complex and D-Phe-Pro-Arg (PPACK) in the PPACK-thrombin structure. A comparison between these and an NMR-derived structure is carried out and discussed.

IT **141650-30-8D**, ternary complex with hirugen and thrombin
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(structure of, antithrombotic activity in relation to)

L7 ANSWER 23 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:620485 HCAPLUS
DOCUMENT NUMBER: 119:220485
TITLE: Structure of human Des(1-45) factor Xa at 2.2 .ANG. resolution
AUTHOR(S): Padmanabhan, Kaillathe; Padmanabhan, K. P.; Tulinsky, A.; Park, Chang H.; Bode, W.; Huber, R.; Blankenship, D. T.; Cardin, A. D.; Kisiel, W.
CORPORATE SOURCE: Dep. Chem., Michigan State Univ., East Lansing, MI, 48824-1322, USA
SOURCE: J. Mol. Biol. (1993), 232(3), 947-66
CODEN: JMOBAK; ISSN: 0022-2836
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The structure of a large mol. fragment of factor Xa that lacks only a Gla (.gamma.-carboxyglutamic acid) domain (N-terminal 45 residues) has been solved by x-ray crystallog. and refined at 2.2 .ANG. resoln. to a crystallog. R-value of 0.168. The fragment identity was clearly established by automated Edman degrdn. X-ray structure anal. confirmed the biochem. characterization and also revealed that the N-terminal epidermal growth factor (EGF)-like domain is flexibly disordered in crystals. The second EGF module, however, is positionally ordered making contacts with the catalytic domain. The overall folding of the catalytic domain is similar to that of .alpha.-thrombin, excluding the insertion loops of the latter with respect to simpler serine proteinases. The C-terminal arginine of the A-chain interacts in a substrate-like manner with the SI specificity site of the active site of a crystallog. neighboring mol. Based on this interaction and the structure of D-PheProArg methylene-thrombin, a model of the commonly used dansylGluGlyArg methylene inhibitor-factor Xa interaction is proposed. The region of factor Xa corresponding to the fibrinogen recognition site of thrombin has a reversed elec. polarity to the anion binding fibrinogen recognition site of thrombin but possesses a site similar to the Ca2+ binding site of trypsin and other serine proteinases. The structure of the C-terminal EGF domain of factor Xa is the first to be detd. crystallog. Its folding has been comprehensively compared with similar domains detd. by NMR. Although the A-chain makes 44 contacts at less than 3.5 .ANG. with the catalytic domain, only 16 involve the EGF module. In addn., the A-chain makes 30 intermol. contacts with a neighboring catalytic domain.
IT **69024-84-6**
RL: BIOL (Biological study)
(des(1-45) blood-**coagulation** factor Xa of human inhibition by, structural model of)

L7 ANSWER 24 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:514687 HCAPLUS
DOCUMENT NUMBER: 119:114687
TITLE: Active site-blocked factor Xa prevents thrombus formation in the coronary vasculature in parallel with inhibition of extravascular **coagulation** in a canine **thrombosis** model
AUTHOR(S): Benedict, Claude R.; Ryan, Jane; Todd, Jerry; Kuwabara, Keisuke; Tijburg, Pim; Cartwright, Joiner, Jr.; Stern, David
CORPORATE SOURCE: Med. Sch., Univ. Texas, Houston, TX, 77225, USA
SOURCE: Blood (1993), 81(8), 2059-66
CODEN: BLOOAW; ISSN: 0006-4971

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Factor Xa is a central **procoagulant** enzyme linking the intrinsic and extrinsic activation mechanisms to the final common pathway of **coagulation**. To assess the factor Xa contribution to the pathol. of **thrombosis**, studies were performed in a canine coronary **thrombosis** model. Thrombus formation was initiated by the application of elec. current via a needle electrode placed in the lumen of the left circumflex coronary artery. When a 50% occlusion of the vessel developed, the current was stopped and animals were given an i.v. bolus of saline, bovine glutamylglycinylarginyl-factor Xa (Xai; competitive inhibitor of factor Xa assembly into the prothrombinase complex), Factor X, or heparin. Animals infused with saline or factor X (300 .mu.g/kg) developed a total occlusion of the vessel due to a fibrin/blood platelet thrombus in 70 min (36 of 36 animals) or 74 min (8 of 8 animals), resp. Xai prevented the thrombus formation completely at a dose of 300 .mu.g/kg (8 of 8 animals). As the dose of Xai was decreased, its antithrombotic effect was diminished, with a potency rate of only 2 of 6 animals at a dose of 90 .mu.g/kg. Xai at 300 .mu.g/kg prevented the accumulation of 125I-fibrinogen/fibrin at the site of the coronary thrombus by .apprx.63% and decreased the deposition of 111In-labeled platelets by .apprx.57%. Hemostatic parameters of animals infused with Xia showed prolongation of the prothrombin time and dose-dependent increases of extravascular bleeding tendency. Thus, factor Xa has a relatively important role in thrombus formation and extravascular hemostasis.

IT **65113-67-9**
RL: BIOL (Biological study)
(as factor Xa inhibitor, coronary **thrombosis** and blood **coagulation** responses to)

L7 ANSWER 25 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1993:116752 HCAPLUS
DOCUMENT NUMBER: 118:116752
TITLE: Inhibition of blood **coagulation** with modified factor VII
INVENTOR(S): Berkner, Kathleen L.; Petersen, Lars Christian
PATENT ASSIGNEE(S): Zymogenetics, Inc., USA; Novo Nordisk A/S
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 9
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9215686 | A1 | 19920917 | WO 1992-US1636 | 19920228 |
| W: AT, AU, BB, BG, BR, CA, CH, CS, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, PL, RO, RU, SD, SE, US | | | | |
| RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FR, GA, GB, GN, GR, IT, LU, MC, ML, MR, NL, SE, SN, TD, TG | | | | |
| CA 2103546 | AA | 19920829 | CA 1992-2103546 | 19920228 |
| AU 9214498 | A1 | 19921006 | AU 1992-14498 | 19920228 |
| AU 672357 | B2 | 19961003 | | |
| EP 575464 | A1 | 19931229 | EP 1992-907393 | 19920228 |
| R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, MC, NL, SE | | | | |
| JP 06504678 | T2 | 19940602 | JP 1992-507422 | 19920228 |
| HU 71572 | A2 | 19951228 | HU 1993-2438 | 19920228 |
| HU 218890 | B | 20001228 | | |

| | | | | |
|---|---|---|---|---|
| US 6039944 | A | 20000321 | US 1995-464233 | 19950605 |
| AU 9671920 | A1 | 19970206 | AU 1996-71920 | 19961122 |
| AU 703760 | B2 | 19990401 | | |
| US 6168789 | B1 | 20010102 | US 1998-189607 | 19981110 |
| US 6183743 | B1 | 20010206 | US 1999-378907 | 19990820 |

PRIORITY APPLN. INFO.:

| | | |
|---|---|---|
| US 1991-662920 | A2 | 19910228 |
| WO 1992-US1636 | A | 19920228 |
| US 1993-65725 | B2 | 19930521 |
| WO 1994-US5779 | A2 | 19940523 |
| US 1994-327690 | A3 | 19941024 |
| US 1995-475845 | A2 | 19950607 |
| US 1996-660289 | A3 | 19960607 |
| US 1997-871003 | A3 | 19970606 |

AB A method for inhibiting blood **coagulation** comprises administering to a patient a Factor VII modified at its catalytic center such that its ability to activate **Factors** X or **IX** is inhibited. The modified Factor VII may be prepd. by reaction with a serine protease inhibitor such as a peptide halomethyl ketone, or by culture of transgenic cells. A gene encoding [Ala-344]Factor VII was prepd. and expressed in BHK 570 cells. In a **clotting** assay mixt. contg. Factor VII-deficient plasma and thromboplastin, addn. of this Factor VII analog had no effect on **clotting** time. The analog was shown to compete with unaltered Factor VII for tissue factor.

IT **69024-84-6**
RL: BIOL (Biological study)
(Factor VII modified with, as **anticoagulant**)

IT **9001-25-6**, Blood-**coagulation** factor VII
RL: BIOL (Biological study)
(inactivated by mutagenesis or chems., as **anticoagulant**)

IT **9001-28-9**, **Factor IX 9001-29-0**,
Factor X
RL: BIOL (Biological study)
(modified **Factor** VII unable to activate, as **anticoagulant**)

L7 ANSWER 26 OF 51 HCAPLUS COPYRIGHT 2001 ACS

| | |
|---|---|
| ACCESSION NUMBER: | 1992:587123 HCAPLUS |
| DOCUMENT NUMBER: | 117:187123 |
| TITLE: | Active-site-selective labeling of blood **coagulation** proteinases with fluorescence probes by the use of thioester peptide chloromethyl ketones. II. Properties of thrombin derivatives as reporters of prothrombin fragment 2 binding and specificity of the labeling approach for other proteinases |
| AUTHOR(S): | Bock, Paul E. |
| CORPORATE SOURCE: | Blood Serv., Am. Red Cross, Detroit, MI, 48232, USA |
| SOURCE: | J. Biol. Chem. (1992), 267(21), 14974-81<br>CODEN: JBCHA3; ISSN: 0021-9258 |
| DOCUMENT TYPE: | Journal |
| LANGUAGE: | English |

AB The behavior of an array of fluorescent human .alpha.-thrombin derivs. in reporting binding of the fragment 2 domain of prothrombin was characterized as a representative application of the active-site-selective labeling approach to studies of blood **coagulation** proteinase regulatory interactions. An array of 16 thrombin derivs. was prepd. by affinity labeling of the proteinase active site with the thioester peptide chloromethyl ketones N.alpha.-[(acetylthio)acetyl]-D-Phe-Pro-Arg-CH2Cl or N.alpha.-[(acetylthio)acetyl]-D-Phe-Phe-Arg-CH2Cl, followed by selective

modification of the NH2OH-generated thiol group on the covalently incorporated inhibitors with each of eight thiol-reactive fluorescence probes. The changes in probe fluorescence intensity of the derivs., signaling changes in the environment of the catalytic site assocd. with fragment 2 binding, appeared to be a unique and unpredictable function of the structure of the probe and the connecting peptide. These results demonstrated the utility of the labeling approach for overcoming the problem of not being able to predict which fluorescent label will provide the most useful proteinase deriv. for investigating an interaction by enabling a greater variety of them to be prepd. and screened for those with the most desirable properties. To det. whether the approach could be extended to other proteinases, the specificity of labeling with the fluorescence probe iodoacetamide, 5-(iodoacetamido)fluorescein, by use of the two thioester inhibitors was evaluated for several other blood **coagulation** proteinases and related trypsin-like enzymes. All of the proteinases were labeled in an active-site-selective manner. The combined results of quantitating the labeling reactions for the proteinase and inhibitor combinations studied thus far showed active-site-specific incorporation of 0.98 mol of inhibitor/mol of active sites and 0.92 mol of probe/mol of active sites, representing an overall .gtoreq.93% site-specificity of labeling. These results demonstrated the broad applicability of the labeling approach for fluorescence studies of proteinases that differ greatly in their catalytic specificities.

IT **143756-48-3**
RL: BIOL (Biological study)
(blood-**coagulation** factors and other serine proteinases active site affinity labeling by, for selective modification with thiol-reactive fluorescent probe in hydroxylamine presence)

IT **37316-87-3**, Blood-**coagulation factor IXa**
RL: BIOL (Biological study)
(selective labeling of active site of, with thiol-reactive fluorescent probe, affinity labeling with thioester peptide chloromethyl ketones in)

L7 ANSWER 27 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1992:566473 HCAPLUS
DOCUMENT NUMBER: 117:166473
TITLE: Active-site-selective labeling of blood **coagulation** proteinases with fluorescence probes by the use of thioester peptide chloromethyl ketones. I. Specificity of thrombin labeling
AUTHOR(S): Bock, Paul E.
CORPORATE SOURCE: Blood Serv., Am. Red Cross, Detroit, MI, 48232, USA
SOURCE: J. Biol. Chem. (1992), 267(21), 14963-73
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In a new strategy for labeling the active sites of serine proteinases with fluorescence probes (Bock, P. E., 1988), a thioester peptide chloromethyl ketone inhibitor is incorporated into the enzyme active center and used to produce a unique thiol group which provides a site for selective chem. modification with any one of many thiol-reactive fluorescence probes. This approach was developed to increase the opportunities for identifying fluorescent proteinase derivs. that act as reporters of binding interactions by allowing a large no. of derivs., representing a broad range of probe spectral properties, to be readily prepd. In the studies described here, the specificity of the labeling approach was evaluated quant. for the labeling of human .alpha.- and .beta./.gamma.-thrombin with

the thioester peptide chloromethyl ketones N.alpha.-[(acetylthio)acetyl]-D-Phe-Pro-Arg-CH2Cl and N.alpha.-[(acetylthio)acetyl]-D-Phe-Phe-Arg-CH2Cl, and the thiol-reactive fluorescence probe, 5-(iodoacetamido)fluorescein. Irreversible inactivation of thrombin by the inhibitors was accompanied by incorporation of 0.98 mol/mol of the thioester group into the active site, independent of a 470-fold difference between the thioester peptide chloromethyl ketones in the bimol. rate consts. of .alpha.-thrombin affinity labeling. Subsequent mild treatment of the covalent thrombin-inhibitor complexes with NH2OH in the presence of 5-(iodoacetamido)fluorescein resulted in generation of the thiol group together with its selective modification and incorporation of 0.96 mol of probe/mol of active sites. The incorporated label was localized to a 9000 mol. wt. region of .alpha.- and .beta./.gamma.-thrombin contg. the catalytic site histidine residue. Evaluation of competing, side reactions showed that they did not significantly compromise the active site specificity of labeling. These results demonstrated equiv., active-site-selective fluorescence probe labeling of .alpha.- and .beta./.gamma.-thrombin by use of either of the thioester peptide chloromethyl ketones, with a site specificity of .gtoreq.94%.

IT **143756-48-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and thrombin isoforms of human active site affinity labeling by, for selective modification with thio-reactive fluorescent probe in hydroxylamine presence)

IT **74392-49-7**
RL: RCT (Reactant)
(reaction of, with succinimidyl(acetylthio)acetate)

L7 ANSWER 28 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:38439 HCAPLUS
DOCUMENT NUMBER: 114:38439
TITLE: Peptidylchloromethyl ketone substrates for the detection of catalytically active serine proteases byimmuno assay
INVENTOR(S): Mann, Kenneth G.; Williams, Brady; Tracy, Russell P.
PATENT ASSIGNEE(S): University of Vermont and State Agricultural College, USA
SOURCE: PCT Int. Appl., 55 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 9003577 | A1 | 19900405 | WO 1989-US4192 | 19890926 |
| W: JP | | | | |
| RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| EP 436654 | A1 | 19910717 | EP 1989-911689 | 19890926 |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| JP 04501460 | T2 | 19920312 | JP 1989-510877 | 19890926 |
| US 6242173 | B1 | 20010605 | US 1992-833646 | 19920207 |

PRIORITY APPLN. INFO.: US 1988-252506 A 19880930
WO 1989-US4192 W 19890926
OTHER SOURCE(S): MARPAT 114:38439

AB Substituted peptidyl-chloromethyl ketone derivs. are irreversible inhibitors of serine proteinases. The peptide (1-3 amino acids) gives the compd. specificity for the active site of a particular proteinase.

Substitution with a reporting group (e.g. biotin, a fluorophore) allows these substrates to be used in immunoassays for catalytically active serine proteinases. These reagents measure active sites rather than cross-reacting material (e.g. zymogens) and are therefore particularly suitable for the detn. of serine proteinase activity of blood **coagulation** factors. Biotinyl-.epsilon.-aminocaproyl-D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone (BC-PPACK) was synthesized by std. chem. and coupled to tissue-type plasminogen activator (tPA) to give tPA-BCPPACK. This was bound to avidin coated microtier plates and the bound tPA measured by immunoassay using peroxidase-coupled antibody. The std. curve showed a lower limit of sensitivity of 2 ng tPA/mL with test samples of 500 ng tPA/mL accurately measured.

IT **69024-84-6 104302-68-3 121593-24-6**
**121593-25-7 121606-84-6 130075-50-2**
**130290-58-3 130356-92-2**
RL: BIOL (Biological study)
(active site-specific fluorescent reagent for serine proteinases, immunoassays in relation to)

IT **37316-87-3**, Blood **coagulation factor IXa**
RL: ANT (Analyte); ANST (Analytical study)
(detn. of, active site-specific chloromethylketones for, immunoassays using)

IT **121593-20-2P 130290-57-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reactions of, in prepn. serine proteinase active site-specific peptidyl chloromethyl ketones)

IT **121593-21-3P 121596-24-5P**
RL: PREP (Preparation)
(prepn. of, as active site-specific fluorescent reagent for serine proteinases)

IT **130290-55-0P**
RL: PREP (Preparation)
(prepn. of, as active site-specific reagent for detn. of serine proteinase)

IT **121593-23-5P**
RL: PREP (Preparation)
(prepn. of, as active site-specific reagent for serine proteinases)

IT **71372-26-4 130290-57-2**
RL: RCT (Reactant)
(reactions of, in prepn. serine proteinase active site-specific peptidyl chloromethyl ketones)

L7 ANSWER 29 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1991:2706 HCAPLUS
DOCUMENT NUMBER: 114:2706
TITLE: Direct addition of nonmacromolecular inhibitor for quantitating the active enzyme in a sample
INVENTOR(S): Verheijen, Johan Hendrikus
PATENT ASSIGNEE(S): Nederlandse Organisatie voor Toegepast-Natuurwetenschappelijk Onderzoek, Neth.
SOURCE: PCT Int. Appl., 22 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| WO 9005309 | A1 | 19900517 | WO 1989-NL80 | 19891103 |
| W: JP, US | | | | |
| RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| NL 8802710 | A | 19900601 | NL 1988-2710 | 19881104 |
| EP 396692 | A1 | 19901114 | EP 1989-912141 | 19891103 |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| JP 03503486 | T2 | 19910808 | JP 1989-511200 | 19891103 |
| PRIORITY APPLN. INFO.: | | | NL 1988-2710 | 19881104 |
| | | | WO 1989-NL80 | 19891103 |

AB A method is developed to distinguish an active enzyme from inactive enzyme, complex with endogenous inhibitor, and proenzyme in a sample by using a nonmacromol. inhibitor (org. fluorophosphate, org. sulfonyl fluoride, or peptidyl halomethyl ketone) for enzymes including tissue-type plasminogen activator (t-PA), thrombin, thiol protease, aspartic acid proteases, etc. The inhibitor labeled with a detectable group (preferably biotin), is small enough to rapidly form a complex with the enzyme when added during or virtually directly after isolation of the sample. A kit for carrying out the method is also included. Thus, a polyclonal antibody (against t-PA)-coated microtiter plate well was used to sep. the conjugate of t-PA and biotinated Phe-Pro-Arg chloromethyl ketone from the sample soln. The amt. of bound biotin was monitored photometrically using a streptavidin-horseradish peroxidase system.

IT **9001-92-7D**, Protease, org. derivs.
RL: BIOL (Biological study)
(detn. of active form of, labeled inhibitor binding in)

IT **130690-46-9**
RL: BIOL (Biological study)
(in urokinase detn.)

L7 ANSWER 30 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:545341 HCAPLUS
DOCUMENT NUMBER: 113:145341
TITLE: Preparation of tripeptides as factor VII/VIIA active site inhibitors
INVENTOR(S): Edgington, T. Scott; Pepe, Michael G.
PATENT ASSIGNEE(S): Corvas, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| WO 8909612 | A1 | 19891019 | WO 1989-US1415 | 19890404 |
| W: AU, DK, JP, NO | | | | |
| RW: AT, BE, CH, DE, FR, GB, IT, LU, NL, SE | | | | |
| US 5023236 | A | 19910611 | US 1989-320559 | 19890313 |
| AU 8934135 | A1 | 19891103 | AU 1989-34135 | 19890404 |
| AU 617169 | B2 | 19911121 | | |
| EP 364561 | A1 | 19900425 | EP 1989-904471 | 19890404 |
| R: AT, BE, CH, DE, FR, GB, IT, LI, LU, NL, SE | | | | |
| JP 03502578 | T2 | 19910613 | JP 1989-504381 | 19890404 |
| DK 8906110 | A | 19900206 | DK 1989-6110 | 19891205 |
| NO 8904881 | A | 19891206 | NO 1989-4881 | 19891206 |
| PRIORITY APPLN. INFO.: | | | US 1988-178495 | 19880407 |
| | | | US 1989-320559 | 19890313 |

WO 1989-US1415 19890404
OTHER SOURCE(S): MARPAT 113:145341
AB Chloromethylketone (CMK)-terminal tripeptides (Markush given) are prepd. as specific inhibitors of the tissue factor-activated serine protease **coagulation** factor VII/VIIa (TF:VII/VIIa). H-L-Leu-L-Thr-L-Arg-CMK (prepn. given) inhibited, at 300 .mu.m, the TF:VII/VIIa activity in the human plasma by 75%, and increased the human plasma **clotting** time.
IT **129474-53-9P 129474-60-8P 129474-67-5P**
**129474-72-2P 129474-77-7P 129474-81-3P**
**129474-92-6P 129475-07-6P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrochlorination of)
IT **129474-52-8P 129474-59-5P 129474-65-3P**
**129474-71-1P 129474-76-6P 129474-80-2P**
**129474-91-5P 129474-97-1P 129475-06-5P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction of, antithrombotic agent by)
IT **129474-98-2P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. of hydrochlorination of)
IT **129474-48-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antithrombolytic agent)
IT **129474-55-1P 129474-61-9P 129474-66-4P**
**129474-68-6P 129474-69-7P 129474-73-3P**
**129474-74-4P 129474-78-8P 129474-79-9P**
**129474-82-4P 129474-87-9P 129474-88-0P**
**129474-93-7P 129474-94-8P 129474-95-9P**
**129474-96-0P 129474-99-3P 129475-04-3P**
**129475-08-7P 129704-05-8P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antithrombotic agent)

L7 ANSWER 31 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1990:194282 HCAPLUS
DOCUMENT NUMBER: 112:194282
TITLE: Synthesis of tripeptide chloromethyl ketones and examination of their inhibitory effects on plasmin and plasma kallikrein
AUTHOR(S): Tsuda, Yuko; Teno, Naoki; Okada, Yoshio; Wanaka, Keiko; Bohgaki, Miyako; Hijikata-Okunomiya, Akiko; Okamoto, Utako; Naito, Taketoshi; Okamoto, Shosuke
CORPORATE SOURCE: Fac. Pharm. Sci., Kobe-Gakuin Univ., Kobe, 673, Japan
SOURCE: Chem. Pharm. Bull. (1989), 37(11), 3108-11
CODEN: CPBTAL; ISSN: 0009-2363
DOCUMENT TYPE: Journal
LANGUAGE: English
AB With the aim of obtaining selective synthetic inhibitors of plasmin and plasma kallikrein, D-Ile-Phe-Lys-CH2Cl, Ile-Phe-Lys-CH2Cl, D-Ile-Phe-Arg-CH2Cl, and Ile-Phe-Arg-CH2Cl were synthesized and their inhibitory activity against plasmin, plasma kallikrein, and other trypsin-like serine proteinases was examd. Among them, D-Ile-Phe-Arg-CH2Cl exhibited a highly selective inhibitory activity against plasma kallikrein, yet D-Ile-Phe-Lys-CH2Cl exhibited nearly the same order of inhibitory activity against plasmin as well as plasma kallikrein.
IT **126583-20-8P 126721-38-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)

(prepn. and deprotection of)
IT **126583-14-0P 126642-87-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and inhibition kinetics with plasmin and plasma kallikrein and other serine proteinases)

L7 ANSWER 32 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:608724 HCAPLUS
DOCUMENT NUMBER: 111:208724
TITLE: Inhibition of proteolytic activation of influenza virus hemagglutinin by specific peptidyl chloroalkyl ketones
AUTHOR(S): Garten, Wolfgang; Stieneke, Andrea; Shaw, Elliott; Wikstrom, Peter; Klenk, Hans Dieter
CORPORATE SOURCE: Inst. Virol., Philipps-Univ., Marburg, 3550, Fed. Rep. Ger.
SOURCE: Virology (1989), 172(1), 25-31
CODEN: VIRLAX; ISSN: 0042-6822
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Lysates of cultured cells were analyzed for arginine-specific endoproteases using peptidyl-p-nitroanilides as chromogenic substrates. The enzymes present in MDBK, MDCK, VERO, BHK, and chick embryo cells required lysine-arginine or arginine-arginine pairs as cleavage sites, whereas chorioallantoic membrane cells contained, in addn., an activity that could cleave at a single arginine. The effect of peptidyl chloroalkyl ketones on the activation of the fowl plaque virus hemagglutinin by the proteases specific for paired basic residues was investigated. When virions contg. uncleaved hemagglutinin were incubated with lysates of uninfected cells, cleavage was completely inhibited by peptidyl chloroalkyl ketones contg. paired basic residues at a concn. of 1 mM. In contrast a compd. contg. a single arginine had no inhibitory activity. When dibasic peptidyl chloroalkyl ketones were added to infected cell cultures, cleavage of hemagglutinin and multiple cycles of virus replication were inhibited at 10 mM. However, a 100-200-fold increase of the inhibitory activity in intact cells could be achieved by N-terminal acylation. These studies suggest a potential role of peptidyl chloroalkyl ketones as antiviral agents.
IT **9001-92-7**, Protease
RL: BIOL (Biological study)
(arginine-specific, influenza virus hemagglutinin posttranslational cleavage by, peptidyl chloroalkyl ketones inhibition of, virus replication in relation to)
IT **69024-80-2 69056-47-9 123496-54-8 123539-54-8**
RL: BIOL (Biological study)
(influenza virus hemagglutinin proteolytic activation inhibition by)

L7 ANSWER 33 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:590099 HCAPLUS
DOCUMENT NUMBER: 111:190099
TITLE: Zymogen/enzyme discrimination using peptide chloromethyl ketones
AUTHOR(S): Williams, E. Brady; Krishnaswamy, Sriram; Mann, Kenneth G.
CORPORATE SOURCE: Health Sci. Complex, Univ. Vermont, Burlington, VT, 05405, USA
SOURCE: J. Biol. Chem. (1989), 264(13), 7536-45
CODEN: JBCHA3; ISSN: 0021-9258

DOCUMENT TYPE: Journal
LANGUAGE: English

AB Glutamylglycinylarginyl chloromethyl ketone, tyrosylglycinylarginyl chloromethyl ketone, and phenylalanylprolylarginyl chloromethyl ketone have been labeled at their N termini using fluorescein, rhodamine-X, lissamine-rhodamine, pyrene, and the 1,5-, 2,5-, and 2,6-dimethylaminonaphthalene-1-sulfonyl moieties. These peptidyl chloromethyl ketones have also been modified by incorporation of biotin and .epsilon.-amino caproyl biotin. The ability of these various chloromethyl ketones to be incorporated into a collection of zymogen-enzyme pairs has been evaluated using a variety of **coagulation** and fibrinolytic proteins. All labeled chloromethyl ketones were efficiently incorporated into the proteases tested, with the exception of urokinase which was refractory to inhibition by phenylalanylprolylarginyl chloromethyl ketone derivs. No modification of any zymogen species was obsd. even under conditions designed to detect minimal reactivity. When enzymes were modified using chloromethyl ketones labeled with .epsilon.-amino caproylbiotin, the modified proteins readily reacted with avidin under a variety of different conditions. The obsd. reactivity with avidin was used in enzyme blotting following electrophoretic resoln. of polypeptide chains and to remove active enzyme present in enzyme-zymogen mixts. These reagents have been used to evaluate the potential for active site expression by the single-chain human factor VII mol. Studies conducted with tissue factor, phospholipids, and Ca using factor X as substrate demonstrate that no activity can be obtained without initial activation of either factor X to factor Xa or factor VII to factor VIIa by an external source. Thus, factor VII is a true zymogen, inert in the blood **clotting** process prior to its cleavage to factor VIIa.

IT **121956-37-4P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and deprotection and reaction with hydroxysuccinylbiotinylaminocaproate)

IT **121593-22-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and deprotection of)

IT **69024-84-6P 104302-68-3P 121593-20-2P**
**121593-23-5P 121593-24-6P 121593-25-7P**
**121593-26-8P 121593-28-0P 121606-84-6P**
**121606-87-9P 121606-88-0P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reaction with blood **coagulation** and fibrinolysis zymogen-proteinase pairs of human, zymogen-enzyme discrimination in relation to)

IT **121593-21-3P 121596-24-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

IT **9001-25-6**, Blood **coagulation** factor VII
**9001-26-7**, Prothrombin **9001-28-9**, Blood **coagulation factor IX 9001-29-0**,
Blood **coagulation** factor X **37316-87-3**, Blood **coagulation factor IXa**
RL: RCT (Reactant)
(reaction of, of human, with biotinylated and fluorescent chloromethyl ketone peptide derivs., zymogen-enzyme discrimination in relation to)

IT **71372-26-4**
RL: RCT (Reactant)
(reaction of, with carboxylfluorescein hydroxysuccinimide ester)

L7 ANSWER 34 OF 51 HCAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1989:188336 HCAPLUS
DOCUMENT NUMBER: 110:188336
TITLE: The properties of peptidyl diazoethanes and chloroethanes as protease inactivators
AUTHOR(S): Wikstrom, Peter; Kirschke, Heidrun; Stone, Stuart; Shaw, Elliott
CORPORATE SOURCE: Friedrich Miescher Inst., Basel, CH-4002, Switz.
SOURCE: Arch. Biochem. Biophys. (1989), 270(1), 286-93
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Earlier work has demonstrated the irreversible inactivation of serine and cysteine proteinases by peptides with a C-terminal chloromethyl ketone group. With a C-terminal diazomethyl ketone, on the other hand, peptides become reagents specific for cysteine proteinases. Reagents with an addnl. Me side chain near the reactive grouping were prepd. and their properties examd. with the goal of decreasing side reactions in a cellular environment. Derivs. of neutral amino acids as well as of lysine and arginine were prepd. The chloroethyl ketones are about 60% less reactive to chem. nucleophiles than the chloromethyl ketones. However, the susceptibilities of the proteases examd. varied remarkably. Cathepsins B and L of the papain family of cysteine proteinases were much less susceptible (about 2 orders of magnitude less) to both peptidyl diazoethyl and chloroethyl ketones. In marked contrast, clostripain, a cysteine proteinase of a sep. family was decisively more susceptible to chloroethyl ketones. The serine proteinases showed a drop in susceptibility to the chloroethyl ketones generally, and this was similar to the drop in chem. reactivity in proceeding from the chloromethyl to the chloroethyl ketone.

IT **9001-92-7**, Protease
RL: BIOL (Biological study)
(peptide chloroethane and diazoethane derivs. inhibitory activity towards)

IT **120240-83-7P 120240-84-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and deprotection of)

IT **120240-75-7P 120267-94-9P 120329-94-4P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and reactivity of, in inactivation of cysteinyl proteinases)

IT **120240-90-6P 121256-01-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

L7 ANSWER 35 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1989:73016 HCAPLUS
DOCUMENT NUMBER: 110:73016
TITLE: Inhibition in purified systems and in human plasma of chimeric plasminogen activators consisting of the amino-terminal region of tissue-type plasminogen activator and the carboxy-terminal region of urokinase-type plasminogen activator
AUTHOR(S): Lijnen, H. R.; Nelles, L.; Van Hoef, B.; De Cock, F.; Collen, D.
CORPORATE SOURCE: Cent. Thromb. Vasc. Res., Univ. Leuven, Louvain, Belg.
SOURCE: Thromb. Haemostasis (1988), 60(2), 247-50
CODEN: THHADQ; ISSN: 0340-6245
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Recombinant chimeric mols. between tissue-type plasminogen activator (t-PA) and single chain urokinase-type plasminogen activator (scu-PA) or 2

chain urokinase-type plasminogen activator (tcu-PA) have intact enzymic properties of scu-PA or tcu-PA towards natural and synthetic substrates (Nelles, L. et al., 1987). Here a comparison was made of the reactivity with inhibitors of both the single-chain and 2-chain variants of recombinant u-PA and 2 recombinant chimeric mols. between t-PA and scu-PA (t-PA/u-PA-s: amino acids 1-263 of t-PA and 144-411 of u-PA; t-PA/u-PA-e: amino acids 1-274 of t-PA and 138-411 of u-PA). Incubation with human plasma in the absence of a fibrin **clot** for 3 h at 37.degree. at equipotent concns. (50% **clot** lysis in 2 h), resulted in significant fibrinogen breakdown (to .apprx.40% of the normal value) for all 2-chain mols., but not for their single-chain counterparts. Preincubation of the plasminogen activators with plasma for 3 h at 37.degree., resulted in complete inhibition of the fibrinolytic potency of the 2-chain mols. but did not alter the potency of the single-chain mols. Inhibition of the 2-chain mols. occurred with a t1/2 of .apprx.45 min. The-2 chain variants were inhibited by the synthetic urokinase inhibitor Glu-Gly-Arg-CH2Cl with apparent 2nd-order rate consts. of 8000-10,000 M-1 s-1, by purified .alpha.2-antiplasmin with 2nd-order rate consts. of .apprx.300 M-1 s-1, and by plasminogen activator inhibitor-1 with 2nd-order rate consts. of .apprx.2 .times. 107 M-1 s-1. It is concluded that the reactivity of single-chain and 2-chain forms of t-PA/u-PA chimeras with inhibitors is very similar to that of the single- and 2-chain forms of intact u-PA.

IT **65113-67-9**
RL: BIOL (Biological study)
(plasminogen activator recombinant chimeras inhibition by, kinetics of)

L7 ANSWER 36 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1988:2547 HCAPLUS
DOCUMENT NUMBER: 108:2547
TITLE: Methyltrypsin: a novel probe of proteinase-inhibitor interactions
AUTHOR(S): Magnotti, Ralph A., Jr.
CORPORATE SOURCE: Dep. Intern. Med., Univ. Cincinnati, Cincinnati, OH, 45267-0585, USA
SOURCE: Biochim. Biophys. Acta (1987), 915(1), 46-52
CODEN: BBACAQ; ISSN: 0006-3002
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Incubation of trypsin with m-guanidinobenzenesulfonic acid Me ester (mGBSOM) under mild conditions resulted in its quant. and specific conversion to N-3-methylhistidinyl-57-trypsin (methyltrypsin). The interactions of .alpha.2-plasmin inhibitor (.alpha.2PI) and .alpha.1-proteinase inhibitor (.alpha.1PI) with the active-site modified enzymes methyltrypsin and dehydroalanyl-195-trypsin (anhydrotrypsin) were studied by thionine difference spectroscopy. For methyltrypsin the dye assocn. const. with .alpha.1PI and .alpha.2PI was 2.7 .times. 105 M-1 and 1.3 .times. 105 M-1, resp., and with anhydrotrypsin, 7.0 .times. 103 M-1 and 3.2 .times. 105 M-1, resp.

IT **69024-84-6**
RL: PRP (Properties)
(assocn. of, with modified trypsin)
IT **9001-92-7**, Proteinase
RL: BIOL (Biological study)
(proteinase inhibitor interactions with, methyltrypsin as probe of)

L7 ANSWER 37 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1987:209841 HCAPLUS
DOCUMENT NUMBER: 106:209841

TITLE: Studies on the effect of serine protease inhibitors on activated contact factors. Application in amidolytic assays for factor XIIa, plasma kallikrein and factor XIa
AUTHOR(S): Tans, Guido; Janssen-Claessen, Truus; Rosing, Jan; Griffin, John H.
CORPORATE SOURCE: Dep. Biochem., Univ. Limburg, Maastricht, NL-6200 MD, Neth.
SOURCE: Eur. J. Biochem. (1987), 164(3), 637-42
CODEN: EJBCAI; ISSN: 0014-2956
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Amidolytic assays were developed to det. factor XIIa, factor XIa, and plasma kallikrein in mixts. contg. variable amts. of each enzyme. The com. available chromogenic p-nitroanilide (Np) substrates Pro-Phe-Arg-NH-Np (S2302 or chromozym PK), Glp-Pro-Arg-NH-Np (S2366), Ile-Glu-(piperidyl)-Gly-Arg-NH-Np (S2337), and Ile-Glu-Gly-Arg-NH-Np (S2222) were tested for their suitability as substrates in these assays. The kinetic parameters for the conversion of S2302, S2222, S2337, and S2366 by .beta. factor XIIa, factor XIa, and plasma kallikrein indicate that each active enzyme exhibits considerable activity towards a no. of these substrates. This precludes direct quantification of the individual enzymes when large amts. of other activated contact factors are present. Several serine proteinase inhibitors were tested for their ability to inhibit those contact factors selectively that may interfere with the factor tested for. Soybean trypsin inhibitor very efficiently inhibited kallikrein, inhibited factor XIa at moderate concns., but did not affect the amidolytic activity of factor XIIa. Therefore, this inhibitor can be used to abolish a kallikrein and factor XIa contribution in a factor XIIa assay. The rate consts. of inhibition (k) of contact activation factors by 3 different chloromethyl ketones are also reported. D-Phe-Pro-Arg-CH2Cl was moderately active against contact factors (k = 2.2 .times. 103 M-1 s-1 at pH 8.3) but showed no differences in specificity. D-Phe-Phe-Arg-CH2Cl was a very efficient inhibitor of plasma kallikrein (k = 1.2 .times. 105 M-1 s-1 at pH 8.3), whereas it slowly inhibited factor XIIa (k = 1.4 .times. 103 M-1 s-1) and factor XIa (k = 0.11 .times. 103 M-1 s-1). Also Dns-Glu-Gly-Arg-CH2Cl (where Dns = 5-dimethylaminonaphthalene-1-sulfonyl) was more reactive toward kallikrein (k = 1.6 .times. 104 M-1 s-1) than towards factor XIIa (k = 4.6 .times. 102 M-1 s-1) and factor XIa (k = 0.6 .times. 102 M-1 s-1). Since Phe-Phe-Arg-CH2Cl is highly specific for plasma kallikrein, it can be used in a factor XIa assay selectively to inhibit kallikrein. Based on the catalytic efficiencies of chromogenic substrate conversion and the inhibition characteristics of serine proteinase inhibitors and chloromethyl ketones, quant. assays were developed for factor XIIa, factor XIa, and kallikrein in mixts. of contact activation factors.

IT **69024-84-6 74392-49-7**
RL: BIOL (Biological study)
(factor XIIa and XIa and kallikrein of human plasma inhibition by, kinetics of)

L7 ANSWER 38 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1986:531234 HCAPLUS
DOCUMENT NUMBER: 105:131234
TITLE: The binding of activated protein C to factors V and Va
AUTHOR(S): Krishnaswamy, Sriram; Williams, E. Brady; Mann, Kenneth G.
CORPORATE SOURCE: Dep. Biochem., Univ. Vermont, Burlington, VT, 05405, USA

SOURCE: J. Biol. Chem. (1986), 261(21), 9684-93
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activated protein C derivatized with the active site-directed fluorophore 2-(dimethylamino)-6-naphthalenesulfonylglutamylglycylarginyl chloromethyl ketone (2,6-DEGR-APC) was used to investigate the binding interactions of the protein to factors V and Va in the presence of phospholipid vesicles. The fluorescence polarization of the 6-dimethylaminonaphthalene-2-sulfonyl moiety increased saturably with increasing phospholipid concns. in the presence or absence of factor V or Va. Differences in the limiting polarization values indicated distinguishable differences in the interactions between 2,6-DEGR-APC and phospholipid in the presence of factor V or Va. The dissocn. const. calcd. for the 2,6-DEGR-APC/phospholipid interaction (7.3 .times. 10-8M) was not significantly altered by factor V but was decreased to 7 .times. 10-9M in the presence of factor Va. The interaction between 2,6-DEGR-APC and factor V or Va was characterized by a 1:1 stoichiometry. The binding of 2,6-DEGR-APC to factor V or Va in the presence of phospholipid could be reduced in a competitive manner by diisopropylphosphofluoridate-treated activated protein C. An anal. of the displacement curves indicated that the binding of 2,6-DEGR-APC was indistinguishable from the binding of diisopropylphosphofluoridate-treated activated protein C. The interaction between 2,6-DEGR-APC and phospholipid-bound factor Va was further examd. by using the isolated subunits of factor Va. Fluorescence polarization changes obsd. with component E of Va (light chain) closely corresponded with the changes obsd. with factor Va, whereas isolated component D (heavy chain) had little influence on the binding of 2,6-DEGR-APC to phospholipid vesicles. The data presented are consistent with the interpretation that component E of factor Va contains a binding site for activated protein C.

IT **65113-67-9**
RL: RCT (Reactant)
(dansylation of)

IT **71372-26-4P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and dansylation of)

IT **71372-20-8P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and deprotection of)

IT **104302-68-3P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

L7 ANSWER 39 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:574529 HCAPLUS
DOCUMENT NUMBER: 103:174529
TITLE: Specificity of activated human protein C
AUTHOR(S): Stone, Stuart R.; Hofsteenge, Jan
CORPORATE SOURCE: Friedrich Miescher Inst., Basel, CH-4002, Switz.
SOURCE: Biochem. J. (1985), 230(2), 497-502
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peptide p-nitroanilide substrates and peptidylchloromethane inhibitors were used to examine the specificity of activated human protein C. Substrates with arginine in the P1 position had the highest activity. The best substrates and inhibitors, as judged by the 2nd-order rate const. for their interaction with the enzyme, had an apolar residue in the P2 position. In contrast with thrombin (Kettner, C.; and Shaw, E., 1981),

activated protein C was able to accommodate large hydrophobic residues such as phenylalanine and leucine in the P2 position. In the P3 position, the enzyme preferred an apolar D-amino acid residue. These results have also indicated a suitable substrate and inhibitor to be used in the assay of functional protein C and thrombomodulin.

IT **65113-67-9 65113-68-0 65319-55-3 69024-81-3 69024-83-5 69056-47-9 71300-96-4 74392-49-7 74392-51-1 98833-84-2**
RL: BIOL (Biological study)
(blood-**coagulation** factor XIVa inhibition by, in human, kinetics of)

L7 ANSWER 40 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:420396 HCAPLUS
DOCUMENT NUMBER: 103:20396
TITLE: The binding of **factor IXa** to cultured bovine aortic endothelial cells. Induction of a specific site in the presence of factors VIII and X
AUTHOR(S): Stern, David M.; Nawroth, Peter P.; Kisiel, Walter; Vehar, Gordon; Esmon, Charles T.
CORPORATE SOURCE: Dep. Med., Columbia Med. Sch., New York City, NY, 10032, USA
SOURCE: J. Biol. Chem. (1985), 260(11), 6717-22
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The affinity of blood-**coagulation factor IXa**, but not **factor IX**, for the bovine aortic endothelial cell surface was increased in the presence of both factors VIII and X. When factor Xa formation was studied in the presence of satg. concns. of factors VIII and X, the half-maximal rate was obsd. at a **factor IXa** concn. of 151 pM. Active site-blocked **factor IXa** (dansyl-Glu-Gly-Arg-**factor IXa**) was a more effective inhibitor of factor X activation (Ki = 124 pM) than was **factor IX** (Ki = 3.0 nM). Radioligand binding studies carried out in the presence of factors VIII and X confirmed the presence of a selective endothelial cell **factor IXa**-binding site with a dissocn. const. of 127 pM. In contrast, when **factor IXa** binding was studied in the absence of other blood-**coagulation** factors, or in the presence of factor VIII (thrombin-activated or unactivated) alone, this new high-affinity site was not obsd. Competitive binding studies indicated that **factor IXa** was 12-fold more effective as an inhibitor of **factor IX**-endothelial cell binding in the presence of factors VIII and X. Consistent with the increased affinity of **factor IXa** binding in the presence of **factors** VIII and X, cell-assocd. **factor IXa coagulant** activity decayed 7-fold more slowly in the presence of these **coagulation** factors. These results demonstrate selective **factor IXa**-endothelial cell binding in the presence of factors VIII and X, suggesting that this interaction could be a physiol. occurrence.

IT **37316-87-3**
RL: PROC (Process)
(aorta endothelial cell binding of, in presence of blood-**coagulation** factors VIII and X)

IT **9001-28-9 37316-87-3D**, dansylglutamylglycylarginine deriv. **69024-84-6D**, reaction products with blood-

**coagulation factor IXa**
RL: BIOL (Biological study)
(blood-**coagulation factor** X activation inhibition by, kinetics of)
IT **9001-29-0**
RL: BIOL (Biological study)
(**procoagulant**, blood-**coagulation factor IXa** binding to aorta endothelial cells in presence of)

L7 ANSWER 41 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1985:84468 HCAPLUS
DOCUMENT NUMBER: 102:84468
TITLE: Characterization of proteases in AHF concentrates: effect on factor VIII:von Willebrand protein as assessed by high pressure gel permeation chromatography
AUTHOR(S): Orthner, Carolyn L.
CORPORATE SOURCE: Plasma Deriv. Lab., American Red Cross Blood Serv. Lab., Bethesda, MD, USA
SOURCE: J. Lab. Clin. Med. (1984), 104(5), 816-28
CODEN: JLCMAK; ISSN: 0022-2143
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antihemophilic factor (AHF) [9001-27-8] concs. were surveyed for amidolytic activity on the chromogenic substrates S2238 [62354-65-8], S2302 [64816-19-9], S2222 [60457-00-3], and S2251 [62354-43-2], which are sensitive to thrombin [9002-04-4], kallikrein [9001-01-8], blood-**coagulation** factor Xa [9002-05-5], and plasmin [9001-90-5], resp. For AHF concs. from 2 manufacturers, the rates of amidolysis of S2238 and S2302 were approx. an order of magnitude greater than the rates of amidolysis of S2222 and S2251. The S2238 and S2302 activities were characterized by quantitating their interactions with specific substrates or inhibitors. The Km for amidolysis of S2238 was 558 .mu.mol/L, which is 80 times higher than for thrombin but in close agreement to the reported value for activated protein C. The S2238 activity was not inhibited by the thrombin-specific inhibitor dansylarginine N-(3-ethyl-1,5-pentanediyl)amide, nor by soybean trypsin inhibitor or micromolar concns. of antithrombin III in the presence of heparin. The S2238 activity was inhibited by D-Phe-Pro-Arg-CH2Cl [71142-71-7], but with an estd. second-order rate const. of 3 .times. 105 mol/L-1 min-1, approx. 1000 times less than for thrombin. These data are consistent with the identity of the S2238 activity as activated protein C. On the other hand, the S2302 activity in AHF concns. was most likely attributable to kallikrein. This was based on the agreement with authentic kallikrein of the Km for S2302 of 154 .mu.mol/L as well as by the rapid inactivation by nanomolar concns. of the kallikrein-specific inhibitor D-Phe-Phe-Arg-CH2Cl [**74392-49-7**]. However, the relative resistance of the S2302 activity to inhibition by soybean trypsin inhibitor or antithrombin III and the partial inhibition by aprotinin [9087-70-1] suggested that a large proportion of the kallikrein was bound to .alpha.2-macroglobulin. This was confirmed by immunopptn. using specific anti .alpha.2-macroglobulin IgG. The potential for proteolysis of blood-**coagulation** factor VIII:von Willebrand protein during its purifn. from AHF concns. was demonstrated, and the proteolyzed factor VIII **coagulant** species was characterized. High-pressure gel permeation chromatog. of purified factor VIII:von Willebrand protein at high ionic strength resulted in 2 sharp peaks of factor VIII **procoagulant** activity. The earlier eluting peak corresponded with the void vol., and the later peak eluted with an apparent mol. wt. of 53,000 daltons.

Immediately after sepn., the 53,000-dalton factor VIII **coagulant** had at least a 100-fold higher specific activity than the factor VIII **coagulant** present in the void vol. However, the 53,000-dalton factor VIII **coagulant** was labile, with a half-life of 80 min. The 53,000 dalton factor VIII **coagulant** was not obsd. when factor VIII:von Willebrand protein was purified from AHF concs. using protease inhibitors.

IT **74392-49-7**
RL: ANST (Analytical study)
(inhibition by, of S2238 amidolysis by antihemophilic factor concs., kinetics of)

IT **9001-92-7**
RL: ANST (Analytical study)
(of antihemophilic factor concs., blood **coagulation** factor VIII:von Willebrand protein detn. by high-pressure gel chromatog. response to)

L7 ANSWER 42 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:546683 HCAPLUS
DOCUMENT NUMBER: 101:146683
TITLE: Inhibition of activated porcine **factor IX** by dansyl-glutamyl-glycyl-arginyl-chloromethylketone
AUTHOR(S): Lollar, Pete; Fass, David N.
CORPORATE SOURCE: Sect. Hematol. Res., Mayo Clin./Found., Rochester, MN, 55905, USA
SOURCE: Arch. Biochem. Biophys. (1984), 233(2), 438-46
CODEN: ABBIA4; ISSN: 0003-9861
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Activated porcine **factor IX** is irreversibly inhibited by an active site histidine-directed serine protease inhibitor, dansylglutamylglycylarginylchloromethylketone (DEGR-CK). The kinetics of inhibition are 2nd order at inhibitor concns. .ltoreq.10-5M. The apparent 2nd-order rate const. (in 0.20M NaCl, pH 8.0) is 1.7 .times. 104 M-1 min-1, which is considerably lower than values reported for factor Xa, thrombin, plasmin, and kallikrein. Reaction of increasing concns. of DEGR-CK with **factor IXa**, followed by anal. of residual enzymic activity, yields 1.2 mol DEGR-CK/mol protein, indicating 1:1 stoichiometry for the DEGR-CK/**Factor IXa** interaction. DEGR-**factor IXa** is a potent **anticoagulant** in vitro. A concn. of 1 nM causes 50% inhibition of the ability of normal porcine-citrated plasma to correct either **factor** VIII- or **factor IX**-deficient plasmas (intrinsic pathway **factors**). In contrast, >100 nM DEGR-**factor IXa** is required to cause 50% inhibition of factor VII (extrinsic pathway) or factor X (common pathway) assays. Activation of porcine factor VIII:C by thrombin in the presence of DEGR-**factor IXa** and phosphatidylcholine-phosphatidylserine vesicles reveals that DEGR-**factor IXa** markedly stabilizes the spontaneous loss of factor VIII:Ca activity as does unmodified **factor IXa**. Apparently DEGR-**factor IXa** incorporates into the intrinsic pathway **factor** X-activator enzymic complex, and also that stabilization of factor VIII:Ca by this complex is independent of the active site of **factor IXa**. Inhibition of **factor IXa** by DEGR-CK results in the first reported irreversible active-site-modified deriv. of this enzyme. DEGR-CK promises to be a useful reagent in the study of the factor X activator complex. Conceivably, its specific **anticoagulant** properties could have

future clin. benefit.
IT **37316-87-3D**, peptide protected deriv. complexes
**69024-84-6D**, blood-**coagulation Factor IXa** complexes
RL: BIOL (Biological study)
(blood **coagulation** in relation to)
IT **69024-84-6**
RL: BIOL (Biological study)
(blood-**coagulation factor IXa** inhibition by)
IT **9001-25-6 9001-28-9 9001-29-0**
RL: BIOL (Biological study)
(blood-**coagulation factor IXa** inhibition by dansylglutamylglycylarginylchloromethylketone in relation to)
IT **37316-87-3**
RL: PROC (Process)
(inhibition of, by dansylglutamylglycylarginylchloromethylketone)

L7 ANSWER 43 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:486231 HCAPLUS
DOCUMENT NUMBER: 101:86231
TITLE: Inhibition of trypsin-like serine proteinases by tripeptide arginyl and lysyl chloromethylketones
AUTHOR(S): Lijnen, H. R.; Uytterhoeven, M.; Collen, D.
CORPORATE SOURCE: Cent. Thrombosis Vasc. Res., Univ. Leuven, Belg.
SOURCE: Thromb. Res. (1984), 34(5), 431-7
CODEN: THBRAA; ISSN: 0049-3848
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Tripeptide derivs. of lysyl- or arginyl-chloromethyl ketone inhibited the serine proteases, trypsin, thrombin, plasmin, blood-**coagulation** factor Xa, urokinase, tissue-type plasminogen activator, and protein Ca. Extremely potent tripeptide inhibitors were obtained for thrombin and trypsin, moderate inhibitors for plasmin and factor Xa, and only weak inhibitors for urokinase, tissue-type plasminogen activator and protein Ca. Thrombin and factor Xa, as well as urokinase and tissue-type plasminogen activator, could be discriminated on the basis of their inhibitory spectrum toward some of these inhibitors.
IT **65113-67-9 91386-14-0**
RL: BIOL (Biological study)
(serine proteinase inhibition by, kinetics of)

L7 ANSWER 44 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1984:435295 HCAPLUS
DOCUMENT NUMBER: 101:35295
TITLE: Measurement of human activated factor X-antithrombin complex by an enzyme-linked differential-antibody immunosorbent assay
AUTHOR(S): Jesty, Jolyon; Morrison, Sidonie A.; Harpel, Peter C.
CORPORATE SOURCE: Dep. Med., State Univ. New York, Stony Brook, NY, 11794, USA
SOURCE: Anal. Biochem. (1984), 139(1), 158-67
CODEN: ANBCA2; ISSN: 0003-2697
DOCUMENT TYPE: Journal
LANGUAGE: English
AB An ELISA was developed for the measurement of the complex of human antithrombin and factor Xa. Rabbit antihuman factor X antibodies are adsorbed to ELISA plates, and samples contg. Xa-antithrombin complex are added. This is followed by the addn. of F(ab')2 fragments of rabbit

antibodies against human antithrombin, previously labeled with alk. phosphatase, and subsequent measurement of the bound labeled antibody by hydrolysis of p-nitrophenylphosphate. The min. level of complex detectable in a sample is .apprx.0.1 nM. The assay was used to follow the generation of factor Xa-antithrombin complex in kinetic situations by the addn. of 1 .mu.M Ile-Glu-Gly-Arg-chloromethylketone to the ELISA sampling buffer, and it was also used in plasma systems, where a 20-fold redn. in the sensitivity of the assay is obsd. This redn. was entirely caused by the plasma factor X. The assay was used to follow generation of the Xa-antithrombin complex in defibrinated plasma upon activation of the **clotting** system with the factor X-activating protein of Russel viper venom, and was compared with the total generation of factor Xa, measured by a radiopeptide assay of factor X activation in the same mixts.

IT **69024-83-5**
RL: ANST (Analytical study)
(activated factor X-antithrombin complexes detn. by ELISA with)

L7 ANSWER 45 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1983:449361 HCAPLUS
DOCUMENT NUMBER: 99:49361
TITLE: Identification of a 31,500-molecular-weight islet cell protease as cathepsin B
AUTHOR(S): Docherty, Kevin; Carroll, Raymond; Steiner, Donald F.
CORPORATE SOURCE: Dep. Biochem., Univ. Chicago, Chicago, IL, 60637, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1983), 80(11), 3245-9
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A method for the prepn. of a radioisotopically labeled active-site directed reagent for proteases, [125I]Tyr-Ala-Lys-ArgCH2Cl (I), is described, and an example of its use as a sensitive method for identifying trypsin-like proteases is provided. This high specific activity reagent was then used in an attempt to identify proteases in rat islets of Langerhans involved in the conversion of proinsulin to insulin. Previous studies have indicated that the endoprotease involved in proinsulin conversion is a cysteine proteinase and that I affinity labels an islet crude granule fraction protein having a mol. wt. of 31,500. The major affinity-labeled proteins of the islet crude granule fraction, when displayed by SDS-gel electrophoresis, have mol. wts. of .apprx.39,000 (5%), 31,500 (53%), and 5000-6000 (37%), with several other minor proteins (<5%) also labeled. The 2 predominant labeled proteins were mainly sol. rather than membrane bound, and they exhibited patterns of competition with various inhibitors that were similar to the pattern shown by the conversion of proinsulin to insulin in vitro. A rabbit antibody to rat liver cathepsin B immunopptd. both affinity-labeled 31,500- and 5000-6000-mol.-wt. proteins, and on the basis of this and structural considerations the 31,500-mol.-wt. cysteine protease is identified as cathepsin B. The 5000-6000-mol.-wt. peptide is an N-terminal, active site cysteine-contg., proteolytic fragment of the 31,500-mol.-wt. protein. Because cathepsin B is not per se a candidate for the proinsulin convertase because of its excessively broad substrate specificity, these studies suggest that a similar enzyme or a modified form of this enzyme is active within the secretory progranules, whereas the more typical cathepsin B may be largely confined to lysosomal contaminants in the granule prepns.

IT **9001-92-7**
RL: BIOL (Biological study)
(of secretory granule, of pancreatic islet, cathepsin B identity to)
IT **86522-70-5P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and proteinase active site labeling by)
IT **69024-80-2**
RL: RCT (Reactant)
(reaction of, with iodinated tyrosine ester)

L7 ANSWER 46 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:421343 HCAPLUS
DOCUMENT NUMBER: 97:21343
TITLE: The dual role of factor VII in blood **coagulation**. Initiation and inhibition of a proteolytic system by a zymogen
AUTHOR(S): Zur, Margalit; Radcliffe, Robert D.; Oberdick, John; Nemerson, Yale
CORPORATE SOURCE: Mount Sinai Sch. Med., City Univ. New York, New York, NY, 10029, USA
SOURCE: J. Biol. Chem. (1982), 257(10), 5623-31
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English
AB A study was conducted to distinguish between the possibilities that the **coagulant** activity of Factor VII zymogen is inherent in the zymogen or due to contamination with Factor VIIa. Factor VII inhibits the activation of [3H]**Factor IX** by **Factor** VIIa when tissue **factor** is limiting, indicating that enzyme and zymogen compete for the cofactor. In contrast, when tissue factor is in excess, the activities are additive. Diisopropyl phosphoryl derivs. of Factor VII and Factor VIIa both inhibit the radioassay for Factor VIIa-tissue factor, the K1/2 of inhibition being 2.8 and 2.0 nM, resp. The rate of incorporation of [3H]diisopropyl fluorophosphate ([3H]DFP) by these proteins is insensitive to trace contamination; pseudo-1st order rate consts. were calcd. for the incorporation of 2 mM DFP into Factor VII and Factor VIIa. These were 0.032 min-1 and 0.130 min-1, resp. Inhibition rates of the **coagulant** activity of the 2 proteins were also detd. in 2 mM DFP. The inhibition kinetics and the rate consts. of incorporation were used to calc. the intrinsic **coagulant** activity of the zymogen. It was nearly 0.8% of that of the enzyme. Factor VII was rendered virtually free of Factor VIIa by incubation with 2 mM DFP for >6 half-lives of Factor VIIa. At this point, Factor VII had .apprx.0.8% the activity of the enzyme. Further, the **coagulant** activity decayed with the rate const. of the zymogen (0.033 min-1). The recent proposal that a ternary complex of tissue factor with Factor VII and Factor Xa (Morrison-Silverberg, S. A.; Jesty, J., 1981) is an essential catalyst in **Factor IX** activation was also explored. These data are not in accord with the existence of such a complex. Factor Xa functions solely as a proteolytic activator of Factor VII, and only the rate of formation of Factor VIIa from Factor VII is dependent on the concn. of Factor Xa. Apparently, the intrinsic **coagulant** activity of Factor VII is adequate to initiate **coagulation**, a process that is then accelerated by the proteolytic conversion of Factor VII to Factor VIIa. The competition between the low activity zymogen and the 120-fold more active enzyme for the cofactor (tissue factor) creates a subtle and previously undescribed mechanism of regulating a proteolytic system.
IT **9001-28-9**
RL: BIOL (Biological study)
(activation of, by blood-**coagulation** factor VIIa, factor VII effect on)
IT **9001-25-6D**, diisopropyl phosphoryl derivs.

RL: BIOL (Biological study)
(blood-**coagulation** factor VIIa **coagulant** activity response to)
IT **69024-83-5**
RL: BIOL (Biological study)
(blood-**coagulation** factor VIIa inactivation by)
IT **9001-25-6**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(**coagulant** activity of)
IT **37316-87-3**
RL: FORM (Formation, nonpreparative)
(formation of, by blood-**coagulation** factor VIIa, factor VII effect on)

L7 ANSWER 47 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1982:30623 HCAPLUS
DOCUMENT NUMBER: 96:30623
TITLE: The inhibition of crotalase, a thrombin-like snake venom enzyme, by several peptide chloromethyl ketone derivatives
AUTHOR(S): Markland, Francis S.; Kettner, Charles; Shaw, Elliott; Bajwa, S. S.
CORPORATE SOURCE: Sch. Med., Univ. Southern California, Los Angeles, CA, 90033, USA
SOURCE: Biochem. Biophys. Res. Commun. (1981), 102(4), 1302-9
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Crotalase (I) was rapidly inhibited by the specific plasma kallikrein inhibitor, prolylphenylalanylarginine chloromethyl ketone (II). Peptide chloromethyl ketones representing the sequences cleaved by thrombin in blood-**coagulation** factor XIII (valylprolylarginine chloromethyl ketone), prothrombin (isoleucylprolylarginine chloromethyl ketone), and the A(.alpha.) chain of fibrinogen (glycylvalylarginine chloromethyl ketone) were much less effective inhibitors of I than was II.
IT **63014-07-3 65113-67-9 65113-68-0**
**69056-47-9 71300-96-4**
RL: BIOL (Biological study)
(crotalase inhibition by, kinetics of)

L7 ANSWER 48 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1981:582948 HCAPLUS
DOCUMENT NUMBER: 95:182948
TITLE: The selective affinity labeling of factor Xa by peptides of arginine chloromethyl ketone
AUTHOR(S): Kettner, Charles; Shaw, Elliott
CORPORATE SOURCE: Biol. Dep., Brookhaven Natl. Lab., Upton, NY, 11973, USA
SOURCE: Thromb. Res. (1981), 22(5-6), 645-52
CODEN: THBRAA; ISSN: 0049-3848
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The prepn. of arginine chloromethyl ketones corresponding to the sequence of prothrombin (-Ile-Glu-Gly-Arg-) hydrolyzed by factor Xa in the prothrombin to thrombin conversion yielded selective and highly effective affinity labels of bovine factor Xa. The most effective affinity label, dansyl-Glu-Gly-ArgCH2Cl, inactivates factor Xa by 50% in 13 min at 2.0 .times. 10-9M. Similar rates of inactivation were obtained for

Ile-Glu-Gly-ArgCH2Cl and Ac-Glu-Gly-ArgCH2Cl at 2.0 .times. 10-8M and for Glu-Gly-ArgCH2Cl at 2.5 .times. 10-7M. Dansyl-Glu-Gly-ArgCH2Cl and Ac-Glu-Gly-ArgCH2Cl were the most selective reagents, inactivating factor Xa 16-22 times more effectively than human plasma kallikrein and .gtoreq.50 times more effectively than thrombin and plasmin.

IT **71372-22-0**
RL: RCT (Reactant)
(acetylation of)

IT **65113-67-9 69024-81-3 69024-84-6 69056-47-9 74392-52-2**
RL: BIOL (Biological study)
(blood-**coagulation** factor Xa affinity labeling and inhibition by)

IT **9001-26-7**
RL: BIOL (Biological study)
(peptide of, blood-**coagulation** factor Xa hydrolysis of, affinity labeling in relation to)

IT **69024-83-5P 79494-42-1P 79494-43-2P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and blood-**coagulation** factor Xa affinity labeling by)

IT **79494-45-4P 79494-46-5P 79494-48-7P**
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and hydrolysis of)

IT **79494-44-3P 79494-47-6P 79548-49-5P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)

IT **71372-22-0**
RL: RCT (Reactant)
(reaction of, with isoleucine blocked deriv.)

L7 ANSWER 49 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1981:512612 HCAPLUS
DOCUMENT NUMBER: 95:112612
TITLE: Cofactor dependence of factor Xa incorporation into the prothrombinase complex
AUTHOR(S): Nesheim, Michael E.; Kettner, Charles; Shaw, Elliott; Mann, Kenneth G.
CORPORATE SOURCE: Hematol. Res. Sect., Mayo Clin./Found., Rochester, MN, 55901, USA
SOURCE: J. Biol. Chem. (1981), 256(13), 6537-40
CODEN: JBCHA3; ISSN: 0021-9258
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Blood-**coagulation** factor Xa, a serine proteinase, was dansylated with the active site-directed inhibitor, dansyl-glutamyl-glycyl-arginyl chloromethyl ketone. The Ca2+-dependent interactions of inactivated factor Xa with its cofactors, phospholipid and activated factor V (factor Va), were studied through alterations of fluorescence polarization values of the dansyl moiety of the modified enzyme. In the presence of phospholipid and Ca2+, factor Va and factor Xa interacted with 1:1 stoichiometry, an interaction characterized by markedly enhanced polarization. The factor Va-independent interaction of factor Xa with phospholipid was also obsd., characterized by dissocn. const. Kd = 2.7 .times. 10-6M and stoichiometry of 66 mol phospholipid/mol factor Xa. The interaction of factor Xa with vesicles in the absence of factor Va exhibited considerably lower polarization values than in the presence of factor Va. These data obtained by direct spectral measurements are in agreement with the inferences drawn previously from studies of kinetics that the prothrombinase complex consists of 1:1 stoichiometric complex of

factor Xa and phospholipid-bound factor Va, and that the enzymic complex assembles in the absence of the natural substrate, prothrombin.

IT **69024-84-6**
RL: BIOL (Biological study)
(blood-**coagulation** factor Xa labeling with)

L7 ANSWER 50 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:545303 HCAPLUS
DOCUMENT NUMBER: 93:145303
TITLE: Effects of proteinase inhibitors on adenylate cyclase
AUTHOR(S): McIlroy, Patrick J.; Richert, Nancy D.; Ryan, Robert J.
CORPORATE SOURCE: Dep. Cell Biol., Mayo Med. Sch. Found., Rochester, MN, 55901, USA
SOURCE: Biochem. J. (1980), 188(2), 423-35
CODEN: BIJOAK; ISSN: 0306-3275
DOCUMENT TYPE: Journal
LANGUAGE: English

AB 7-Amino-1-chloro-3-L-tosylamidoheptan-2-one (I), 1-chloro-4-phenyl-3-L-tosylamidobutan-2-one (II), 1-chloro-4-methyl-3-L-tosylamidopentan-2-one (III), N.alpha.-tosylarginine Me ester (IV), and other low-mol.-wt. proteinase inhibitors blocked hormonally stimulated adenylate cyclase (EC 4.6.1.1) (V) activity in rat ovarian and hepatic membrane prepns., the latter requiring higher concns. Nucleotides did not reactivate the inhibited ovarian prepns., nor did dithiothreitol reverse phenylmethanesulfonyl fluoride-inhibited ovarian V. I, II, and III had 2 effects on human chorionic gonadotropin-stimulated rat ovarian V activity. At low concns. (.ltoreq.0.2 mM), there was an irreversible inhibition of hormonally stimulated V with max. 1st-order inhibitory rate consts. of 0.05-0.08 min-1. At higher concns., the irreversible effect persisted, but there was also a marked decrease in the V initial velocity to 25-50% of control values. IV showed similar effects; at low concns. (.ltoreq.2 mM) it inhibited irreversibly, and at higher concns. it decreased the initial velocity (50% at 10 mM). At higher concns. (>3 mM), IV also inhibited NaF- and guanosine 5'-(.beta.,.gamma.-imido)triphosphate-stimulated V, but in a reversible manner. I inhibited NaF-stimulated V in 2 ways, as for human chorionic gonadotropin-stimulated V, but required 10- to 20-fold higher concns. The low-concn. irreversible effect was explained by a continual inactive .dblharw. active conversion of V during hormone stimulation in which the inactive-to-active conversion is blocked by the inhibitors. The high-concn. effect is a direct one on the active catalytic moiety of V.

IT **69024-84-6**
RL: BIOL (Biological study)
(adenylate cyclase of liver and ovary membranes in response to)

IT **9001-92-7**
RL: BIOL (Biological study)
(low-mol.-wt. inhibitors of, adenylate cyclase response to)

L7 ANSWER 51 OF 51 HCAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1980:175119 HCAPLUS
DOCUMENT NUMBER: 92:175119
TITLE: Effects of N.alpha.-tosyl-L-lysyl-chloromethylketone on the activity of cytotoxic T lymphocytes
AUTHOR(S): Chang, Tse Wen; Eisen, Herman N.
CORPORATE SOURCE: Dep. Biol., Massachusetts Inst. Technol., Cambridge, MA, 02139, USA
SOURCE: J. Immunol. (1980), 124(3), 1028-33
CODEN: JOIMA3; ISSN: 0022-1767

DOCUMENT TYPE: Journal
LANGUAGE: English
AB The lysis of allogeneic target cells by cytotoxic thymus-derived lymphocytes (CTL) was reduced markedly (20-100%) by an irreversible protease [**9001-92-7**] inhibitor, N.alpha.-tosyl-L-lysylchloromethylketone (TLCK) [2364-87-6], (0.2-2.0 .times. 10-4M). Pretreatment of CTL and target cells indicated that TLCK affected primarily CTL, although it also slightly decreased the susceptibility of the target cells. At concns. where TLCK completely blocked CTL lytic activity, it had no effect on the viability of the effector cell population. In addn., the CTL treated with TLCK gradually recovered the cytotoxic activity after 1-4 days, suggesting that TLCK-modified components were replaced. N.epsilon.-Acetyl-TLCK [73359-19-0] and N.epsilon.-succinyl-TLCK [73359-20-3] were synthesized, and they and 20 other protease inhibitors were also tested. Seventeen of the inhibitors did not block CTL activity. Whether the others had any effect could not be detd., because there was only a small difference in the concns. at which they inhibited the cytotoxic reaction and at which they were toxic for the CTL. Apparently, among the 23 inhibitors tested, TLCK was unique: it affects an unknown component, not necessarily a protease, required for cytotoxic activity of CTL. Addn. of TLCK at different steps of the cytolytic sequence (conjugate formation, programming for lysis, and CTL-independent cell lysis) suggested that it affected programming for lysis, not the other steps.
IT **65113-67-9 65319-55-3 69056-47-9**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(cytotoxic T lymphocyte response to)
IT **9001-92-7**
RL: PRP (Properties)
(in T-lymphocyte cytotoxicity)

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E1 THROUGH E118 ASSIGNED

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8          RN   169871-13-0  REGISTRY
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L9 ANSWER 1 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **331664-34-7** REGISTRY
CN L-Phenylalaninamide, 1,1'-(1,5-dioxo-1,5-pentanediyl)bis[L-phenylalanyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
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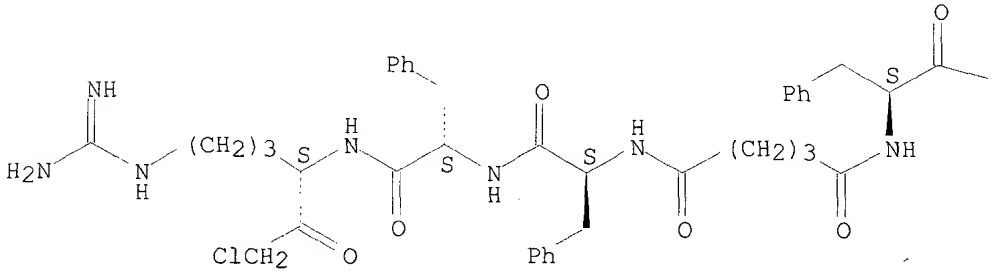
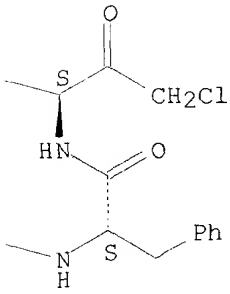
MF C55 H70 Cl2 N12 O8
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B



1 REFERENCES IN FILE CA (1967 TO DATE)
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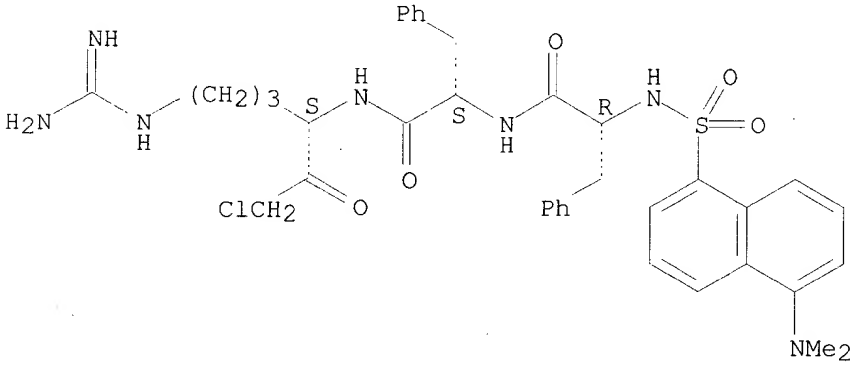
REFERENCE 1: 134:247248

L9 ANSWER 5 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **321680-09-5** REGISTRY
CN L-Phenylalaninamide, N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-D-phenylalanyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C37 H44 Cl N7 O5 S
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
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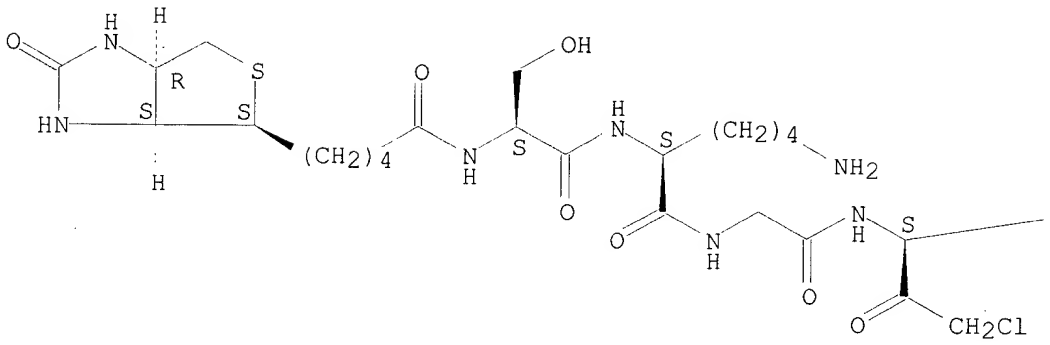
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 134:125963

L9 ANSWER 6 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **201746-19-2** REGISTRY
CN Glycinamide, N-[5-[(3aS,4S,6aR)-hexahydro-2-oxo-1H-thieno[3,4-d]imidazol-4-yl]-1-oxopentyl]-L-seryl-L-lysyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
FS PROTEIN SEQUENCE; STEREOSEARCH
MF C28 H49 Cl N10 O7 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



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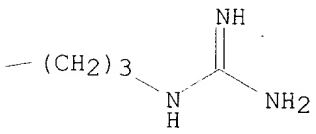

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REFERENCE 1: 128:112217

L9 ANSWER 7 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **200802-98-8** REGISTRY
CN L-Phenylalaninamide, N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-phenylalanyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-(9CI) (CA INDEX NAME)
FS STEREOSEARCH
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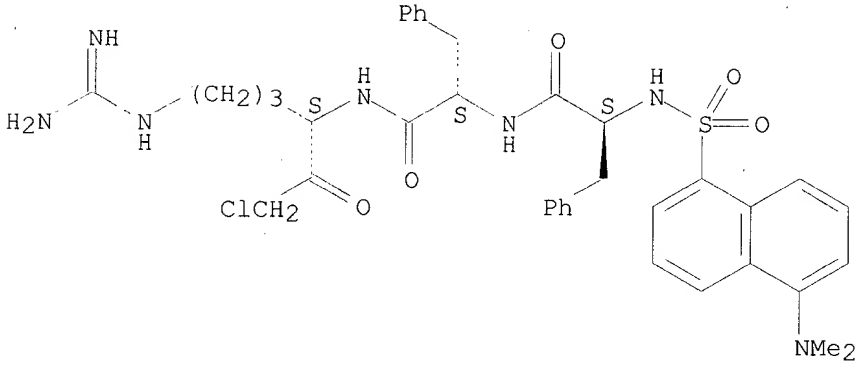
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL

Absolute stereochemistry.



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REFERENCE 2: 132:18788

REFERENCE 3: 130:7391

REFERENCE 4: 129:156938

REFERENCE 5: 128:97711

L9 ANSWER 8 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **169871-13-0** REGISTRY
CN L-Phenylalaninamide, L-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, monohydrochloride, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
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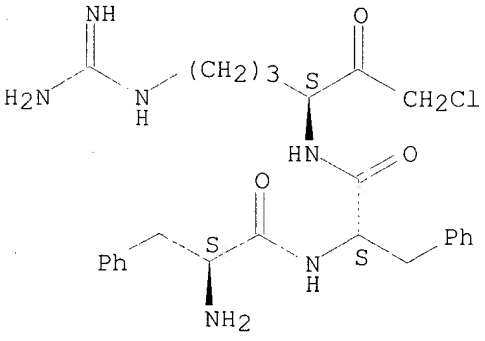
SR CA
LC STN Files: CA, CAPLUS, TOXLIT
CRN (74392-51-1)

Absolute stereochemistry.



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1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:305972

L9 ANSWER 9 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **169388-20-9** REGISTRY
CN L-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-L-phenylalanyl-N-[1-(chloroacetyl)-4-[[imino[[(4-methylphenyl)sulfonyl]amino]methyl]amino]butyl]-, (S)- (9CI) (CA INDEX NAME)
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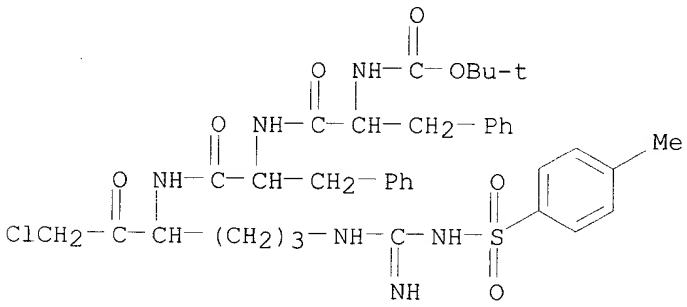
SR CA
LC STN Files: CA, CAPLUS, TOXLIT



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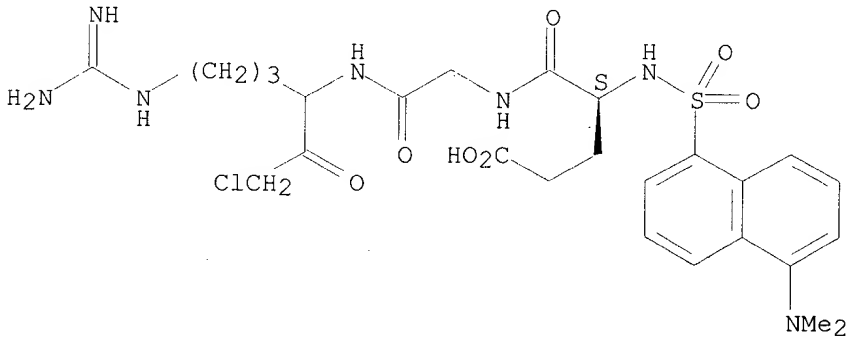
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 123:305972

L9 ANSWER 10 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **155735-17-4** REGISTRY
CN Glycinamide, N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H36 Cl N7 O7 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



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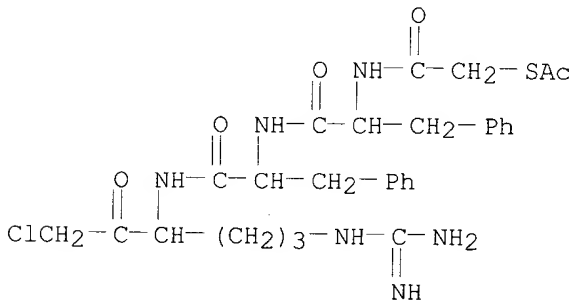
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 121:30502

L9 ANSWER 11 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **143756-48-3** REGISTRY
CN L-Phenylalaninamide, N-[(acetylthio)acetyl]-D-phenylalanyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN L-Phenylalaninamide, N-[(acetylthio)acetyl]-D-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)-
MF C29 H37 Cl N6 O5 S
SR CA
LC STN Files: CA, CAPLUS



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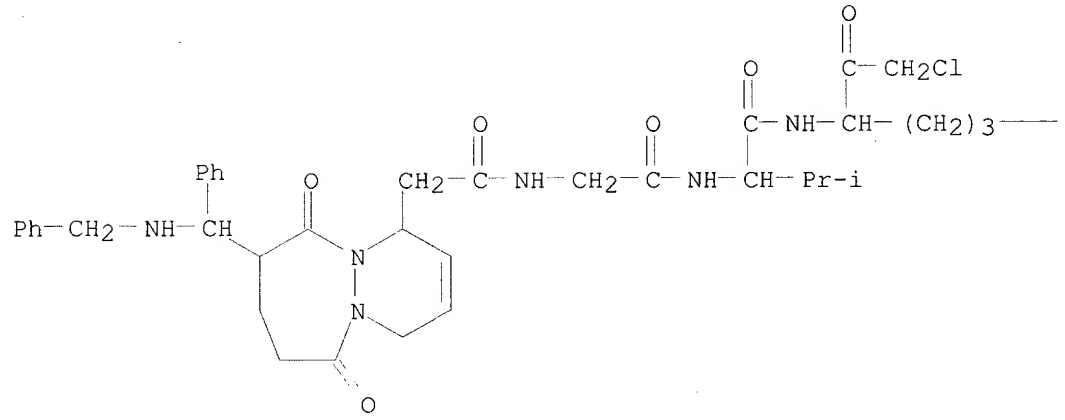
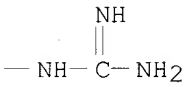
REFERENCE 3: 117:166473

L9 ANSWER 12 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **141650-30-8** REGISTRY
CN L-Valinamide, N-[[1,4,7,8,9,10-hexahydro-6,10-dioxo-9-[phenyl[(phenylmethyl)amino]methyl]-6H-pyridazino[1,2-a][1,2]diazepin-1-yl]acetyl]glycyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, [1R-[1.alpha.(S*),9.beta.(S*)]]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN 6H-Pyridazino[1,2-a][1,2]diazepine, L-valinamide deriv.
FS PROTEIN SEQUENCE
MF C39 H52 Cl N9 O6
SR CA
LC STN Files: CA, CAPLUS, MEDLINE, TOXLIT

PAGE 1-A



PAGE 1-B



3 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

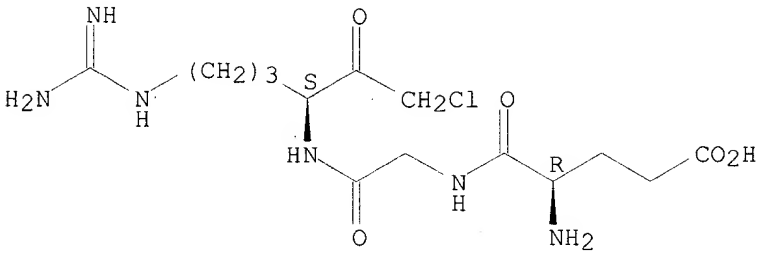
REFERENCE 1: 123:187718

REFERENCE 2: 119:241086

REFERENCE 3: 117:3149

L9 ANSWER 13 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **130690-46-9** REGISTRY
CN Glycinamide, D-.alpha.-glutamyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glycinamide, D-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)-
FS STEREOSEARCH
MF C14 H25 Cl N6 O5
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



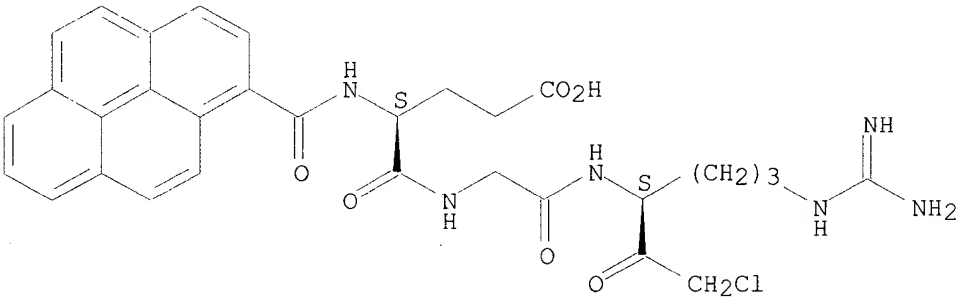
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:30730

REFERENCE 2: 114:2706

L9 ANSWER 14 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **130356-92-2** REGISTRY
CN Glycinamide, N-(1-pyrenylcarbonyl)-L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C31 H33 Cl N6 O6
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

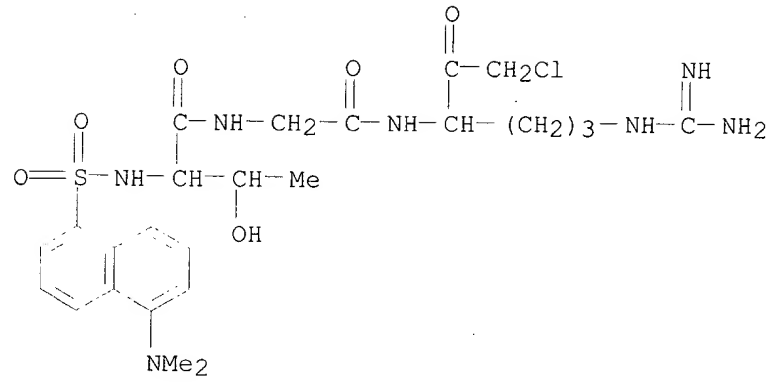
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 114:38439

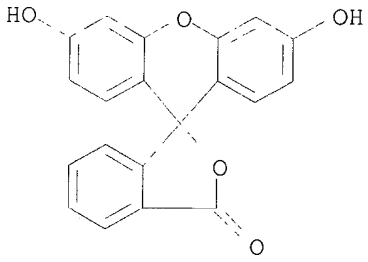
L9 ANSWER 15 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **130290-58-3** REGISTRY
CN Glycinamide, N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-threonyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C25 H36 Cl N7 O6 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

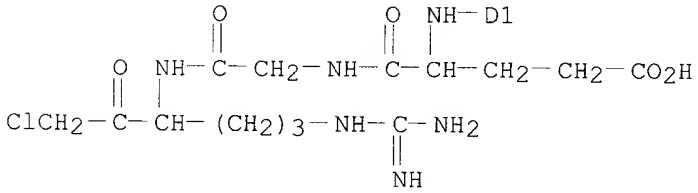


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 114:38439

L9 ANSWER 18 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **130075-50-2** REGISTRY
CN Glycinamide, N-[3',6'-dihydroxy-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-5(or 6)-yl]-L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Spiro[isobenzofuran-1(3H),9'-[9H]xanthene], glycinamide deriv.
MF C34 H35 Cl N6 O10
CI IDS
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

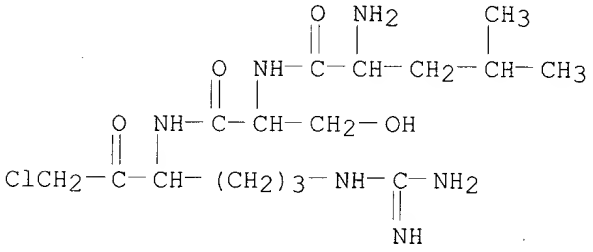




1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 114:38439

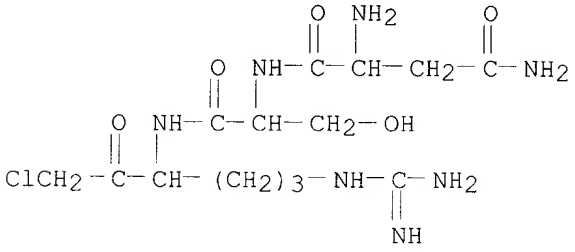
L9 ANSWER 19 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **129704-05-8** REGISTRY
CN L-Serinamide, L-leucyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C16 H31 Cl N6 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 113:145341

L9 ANSWER 20 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **129475-08-7** REGISTRY
CN L-Serinamide, L-asparaginyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, dihydrochloride, (S)- (9CI) (CA INDEX NAME)
MF C14 H26 Cl N7 O5 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL
CRN (129475-04-3)

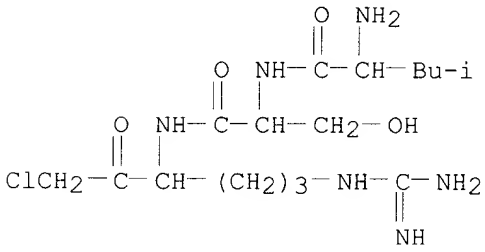


●2 HCl

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 113:145341

L9 ANSWER 24 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **129474-99-3** REGISTRY
CN L-Serinamide, L-leucyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, dihydrochloride, (S)- (9CI) (CA INDEX NAME)
MF C16 H31 Cl N6 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, TOXLIT, USPATFULL
CRN (129704-05-8)

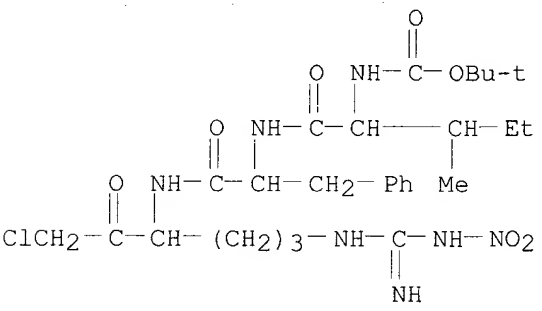


● 2 HCl

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 113:145341

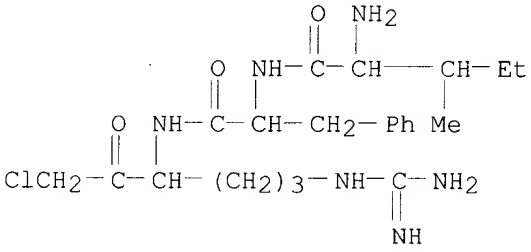
L9 ANSWER 58 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **126721-38-8** REGISTRY
CN L-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-L-isoleucyl-N-[1-(chloroacetyl)-4-[[imino(nitroamino)methyl]amino]butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C27 H42 Cl N7 O7
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 112:194282

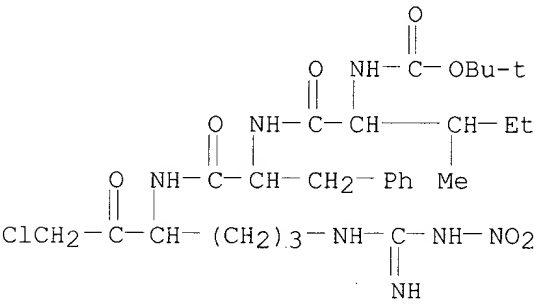
L9 ANSWER 59 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **126642-87-3** REGISTRY
CN L-Phenylalaninamide, L-isoleucyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C22 H35 Cl N6 O3
SR CA
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 112:194282

L9 ANSWER 60 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **126583-20-8** REGISTRY
CN L-Phenylalaninamide, N-[(1,1-dimethylethoxy)carbonyl]-D-isoleucyl-N-[1-(chloroacetyl)-4-[[imino(nitroamino)methyl]amino]butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C27 H42 Cl N7 O7
SR CA
LC STN Files: BEILSTEIN*, CA, CAPLUS
(*File contains numerically searchable property data)



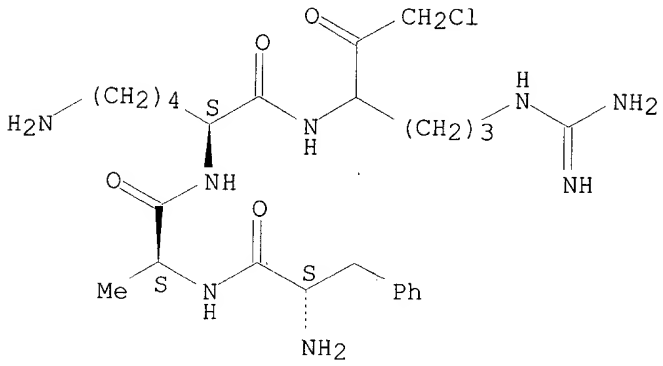
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 112:194282

L9 ANSWER 62 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **123539-54-8** REGISTRY
CN L-Lysinamide, L-phenylalanyl-L-alanyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C25 H41 Cl N8 O4
SR CA
LC STN Files: CA, CAPLUS, TOXLIT

Absolute stereochemistry.

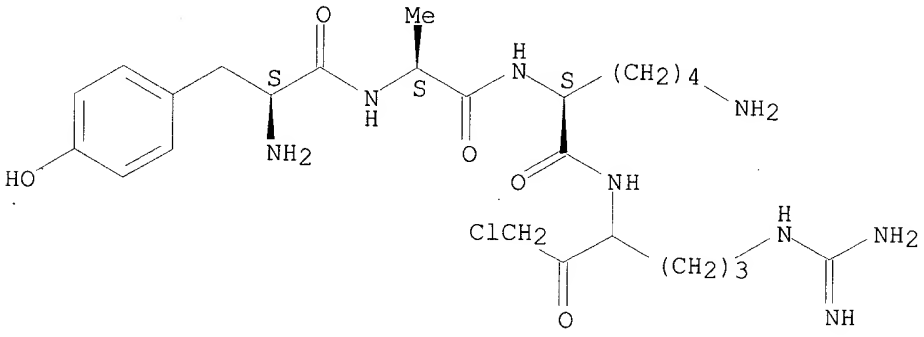


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 111:208724

L9 ANSWER 63 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **123496-54-8** REGISTRY
CN L-Lysinamide, L-tyrosyl-L-alanyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C25 H41 Cl N8 O5
SR CA
LC STN Files: CA, CAPLUS, MEDLINE, TOXLIT

Absolute stereochemistry.



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

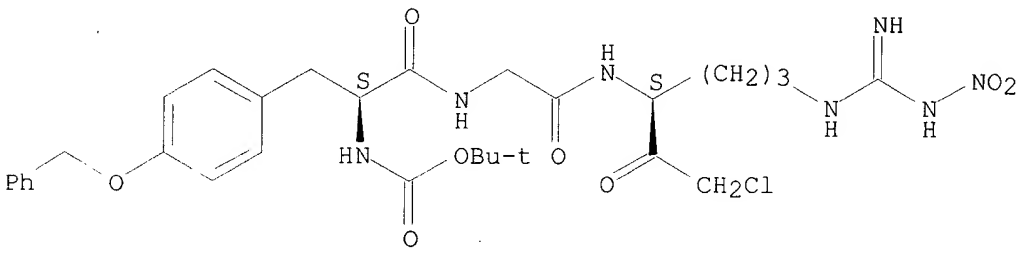
REFERENCE 1: 119:220160

REFERENCE 2: 111:208724

L9 ANSWER 64 OF 111 REGISTRY COPYRIGHT 2001 ACS

RN **121956-37-4** REGISTRY
CN Glycinamide, N-[(1,1-dimethylethoxy)carbonyl]-O-(phenylmethyl)-L-tyrosyl-N-[1-(chloroacetyl)-4-[[imino(nitroamino)methyl]amino]butyl]-, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H40 Cl N7 O8
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



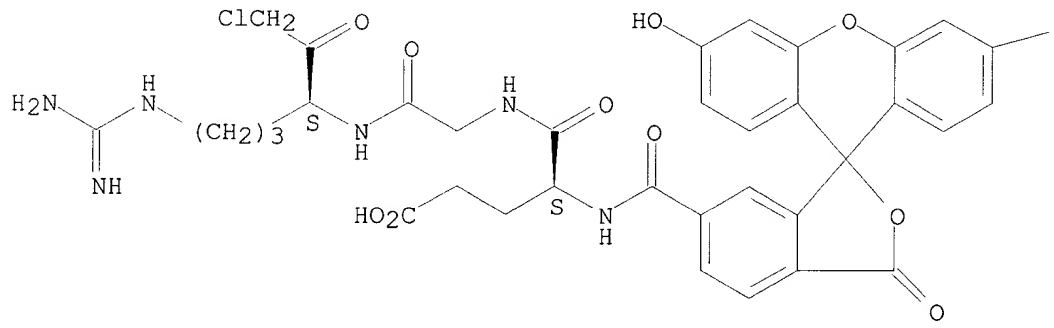
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 111:190099

L9 ANSWER 65 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **121606-88-0** REGISTRY
CN Glycinamide, N-[(3',6'-dihydroxy-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-6-yl)carbonyl]-L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Spiro[isobenzofuran-1(3H),9'-[9H]xanthene], glycinamide deriv.
FS STEREOSEARCH
MF C35 H35 Cl N6 O11
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

PAGE 1-A



PAGE 1-B

—OH

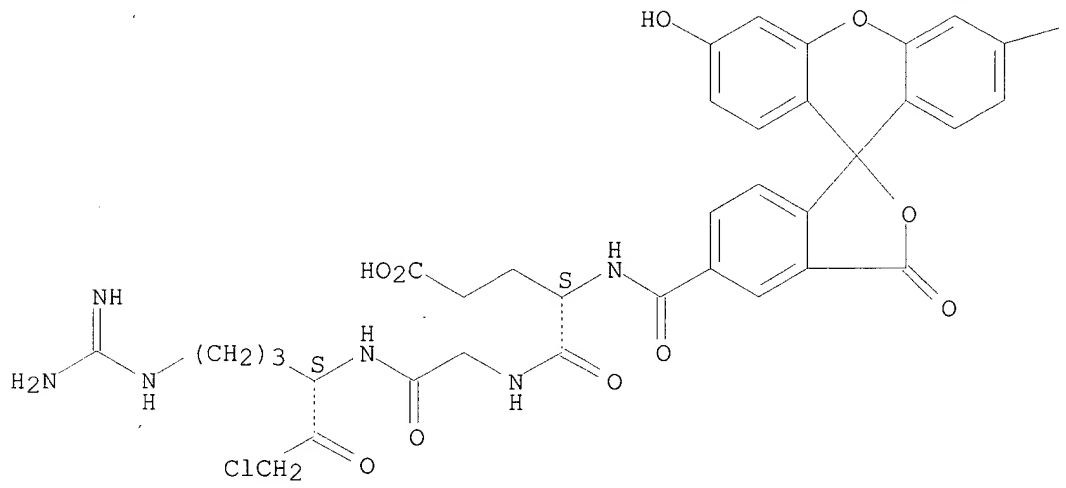
1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 111:190099

L9 ANSWER 68 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **121596-24-5** REGISTRY
CN Glycinamide, N-[(3',6'-dihydroxy-3-oxospiro[isobenzofuran-1(3H),9'-[9H]xanthen]-5-yl)carbonyl]-L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, monohydrochloride, (S)-(9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Spiro[isobenzofuran-1(3H),9'-[9H]xanthene], glycinamide deriv.
FS STEREOSEARCH
MF C35 H35 Cl N6 O11 . Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (121606-87-9)

Absolute stereochemistry.

PAGE 1-A



● HCl

PAGE 1-B

—OH

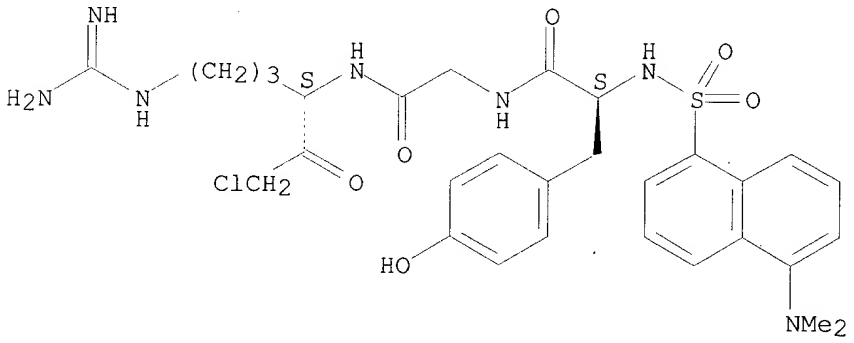
2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 114:38439

REFERENCE 2: 111:190099

L9 ANSWER 69 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **121593-28-0** REGISTRY
CN Glycinamide, N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-tyrosyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H38 Cl N7 O6 S
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

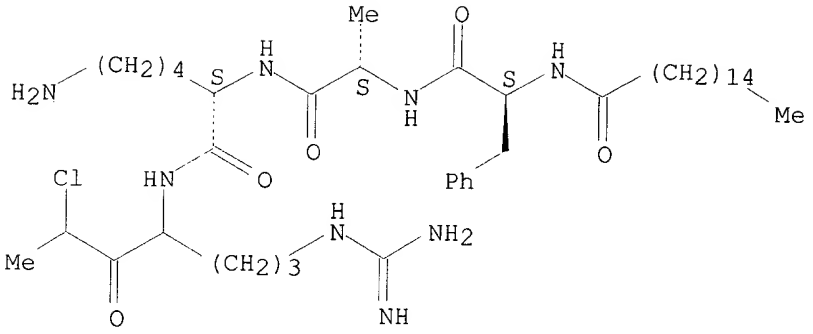


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 111:190099

L9 ANSWER 77 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **121256-01-7** REGISTRY
CN L-Lysinamide, N-(1-oxohexadecyl)-L-phenylalanyl-L-alanyl-N-[1-[3-[(aminoiminomethyl)amino]propyl]-3-chloro-2-oxobutyl]-, dihydrochloride (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C42 H73 Cl N8 O5 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (120267-94-9)

Absolute stereochemistry.



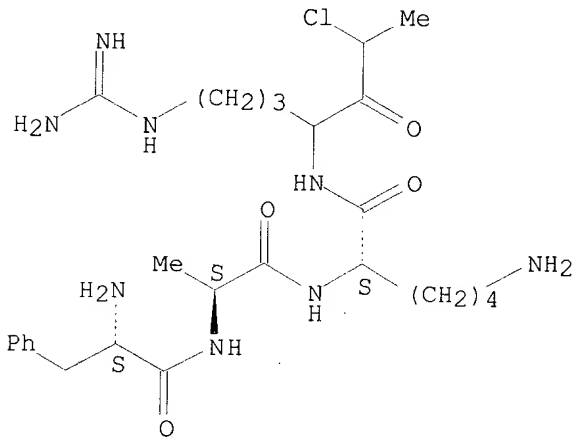
●2 HCl

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 110:188336

L9 ANSWER 78 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **120329-94-4** REGISTRY
CN L-Lysinamide, L-phenylalanyl-L-alanyl-N-[1-[3-[(aminoiminomethyl)amino]propyl]-3-chloro-2-oxobutyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H43 Cl N8 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

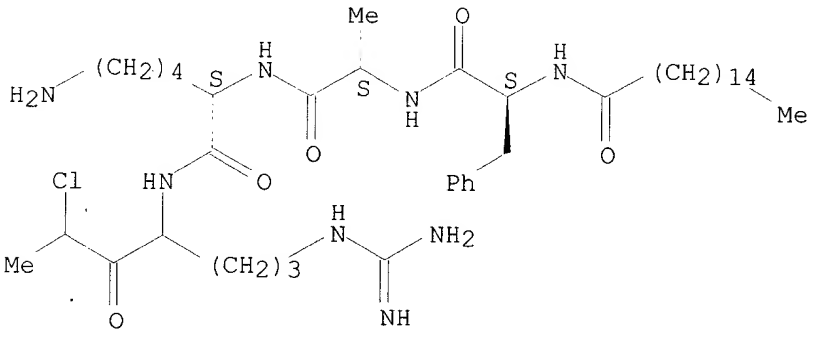


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 110:188336

L9 ANSWER 79 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **120267-94-9** REGISTRY
CN L-Lysinamide, N-(1-oxohexadecyl)-L-phenylalanyl-L-alanyl-N-[1-[3-[(aminoiminomethyl)amino]propyl]-3-chloro-2-oxobutyl]- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C42 H73 Cl N8 O5
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

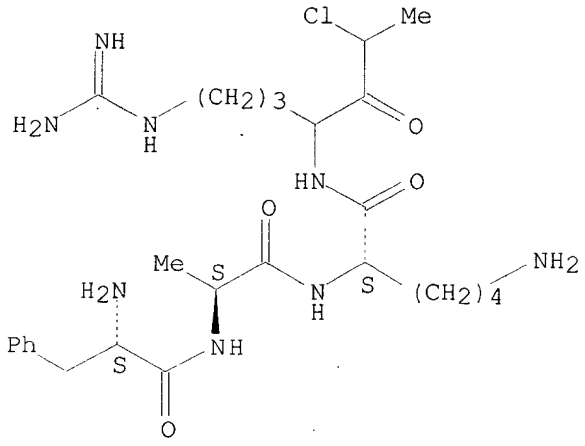


1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 110:188336

L9 ANSWER 80 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **120240-90-6** REGISTRY
CN L-Lysinamide, L-phenylalanyl-L-alanyl-N-[1-[3-[(aminoiminomethyl)amino]propyl]-3-chloro-2-oxobutyl]-, trihydrochloride (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H43 Cl N8 O4 . 3 Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (120329-94-4)

Absolute stereochemistry.



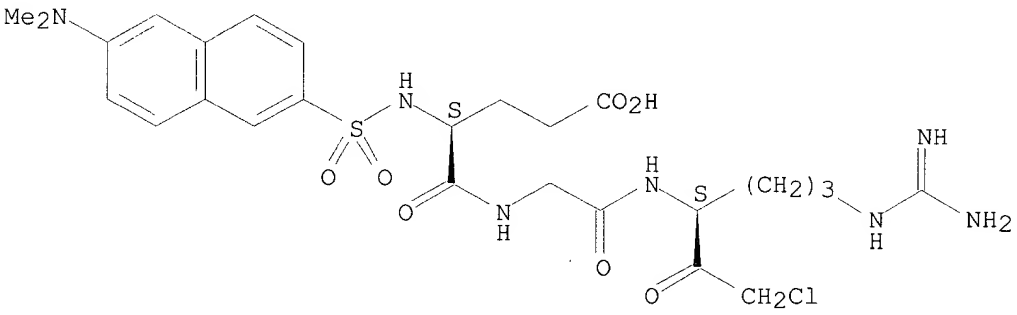
●3 HCl

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 110:188336

L9 ANSWER 84 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **104302-68-3** REGISTRY
CN Glycinamide, N-[[6-(dimethylamino)-2-naphthalenyl]sulfonyl]-L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)-(9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H36 Cl N7 O7 S
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



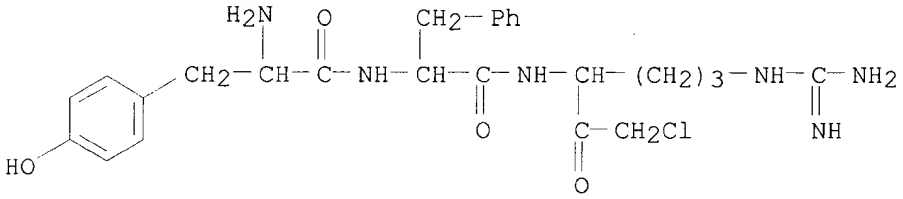
3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 114:38439

REFERENCE 2: 111:190099

REFERENCE 3: 105:131234

L9 ANSWER 85 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **98833-84-2** REGISTRY
CN L-Phenylalaninamide, L-tyrosyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C25 H33 Cl N6 O4
SR CA
LC STN Files: CA, CAPLUS



3 REFERENCES IN FILE CA (1967 TO DATE)
3 REFERENCES IN FILE CAPLUS (1967 TO DATE)

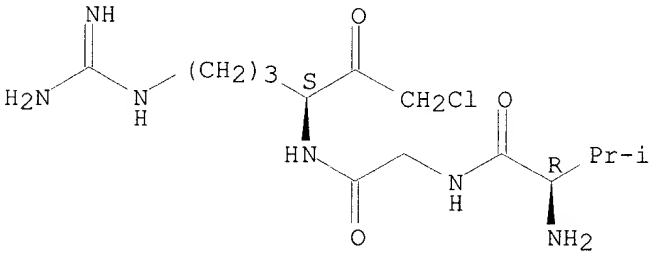
REFERENCE 1: 120:48746

REFERENCE 2: 108:218176

REFERENCE 3: 103:174529

L9 ANSWER 86 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **91386-14-0** REGISTRY
CN Glycinamide, D-valyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glycinamide, D-valyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)-
FS STEREOSEARCH
MF C14 H27 Cl N6 O3
LC STN Files: CA, CAPLUS

Absolute stereochemistry.

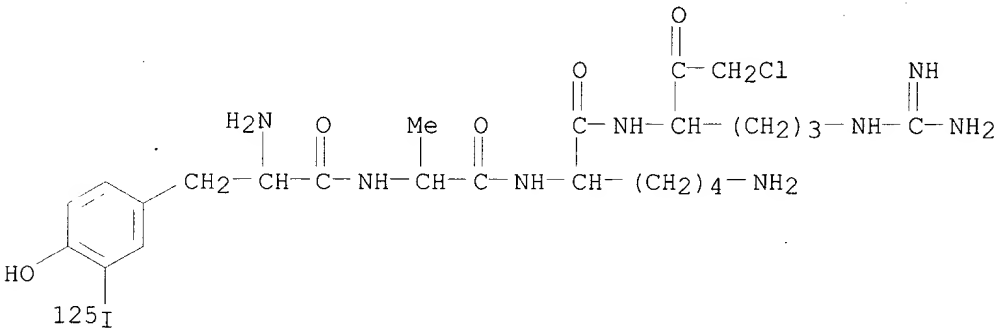


2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 135:30730

REFERENCE 2: 101:86231

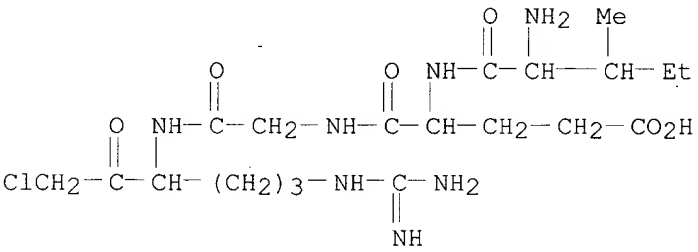
L9 ANSWER 87 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **86522-70-5** REGISTRY
CN L-Lysinamide, 3-(iodo-125I)-L-tyrosyl-L-alanyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C25 H40 Cl I N8 O5
LC STN Files: CA, CAPLUS



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 99:49361

L9 ANSWER 88 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **79548-49-5** REGISTRY
CN Glycinamide, L-isoleucyl-L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, dihydrochloride, (S)- (9CI) (CA INDEX NAME)
MF C20 H36 Cl N7 O6 . 2 Cl H
LC STN Files: CA, CAPLUS
CRN (69024-83-5)



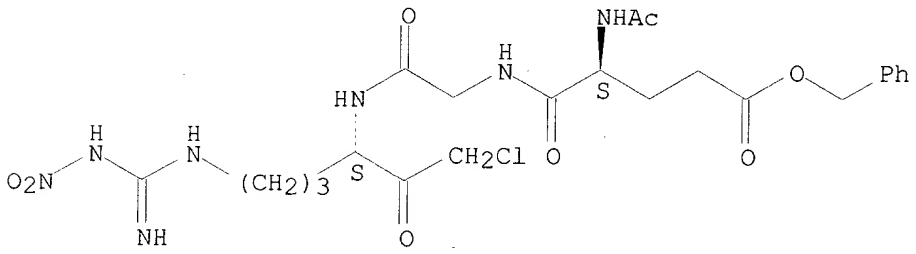
●2 HCl

1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 95:182948

L9 ANSWER 89 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **79494-48-7** REGISTRY
CN Glycinamide, N-acetyl-L-.alpha.-glutamyl-N-[1-(chloroacetyl)-4-[[imino(nitroamino)methyl]amino]butyl]-, phenylmethyl ester, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C23 H32 Cl N7 O8
LC STN Files: CA, CAPLUS

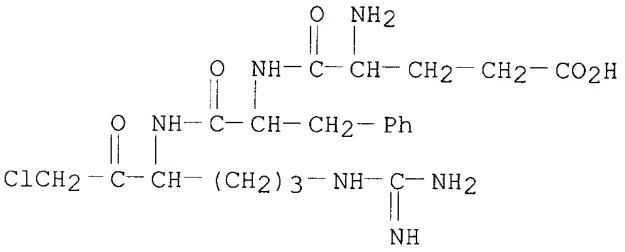
Absolute stereochemistry.



1 REFERENCES IN FILE CA (1967 TO DATE)
1 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 95:182948

L9 ANSWER 96 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **74392-52-2** REGISTRY
CN L-Phenylalaninamide, L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C21 H31 Cl N6 O5
CI COM
LC STN Files: CA, CAPLUS



2 REFERENCES IN FILE CA (1967 TO DATE)
2 REFERENCES IN FILE CAPLUS (1967 TO DATE)

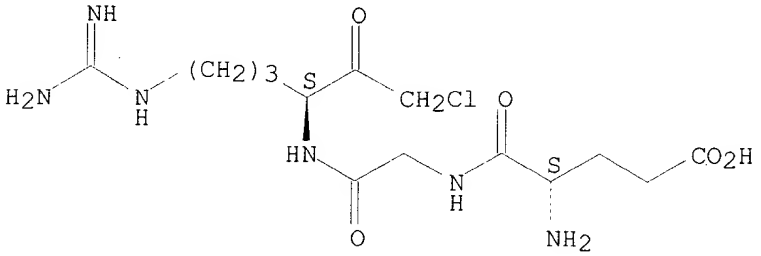
REFERENCE 1: 95:182948

REFERENCE 2: 93:163452

L9 ANSWER 99 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **71372-26-4** REGISTRY
CN Glycinamide, L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, dihydrochloride, (S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH

MF C14 H25 Cl N6 O5 . 2 Cl H
LC STN Files: CA, CAPLUS, CHEMCATS, USPATFULL
CRN (65113-67-9)

Absolute stereochemistry.



●2 HCl

4 REFERENCES IN FILE CA (1967 TO DATE)
4 REFERENCES IN FILE CAPLUS (1967 TO DATE)

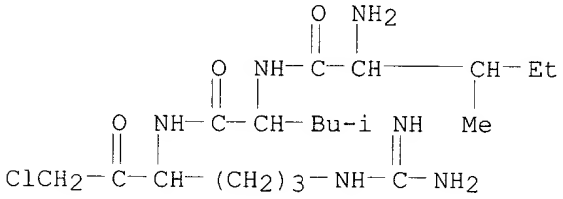
REFERENCE 1: 114:38439

REFERENCE 2: 111:190099

REFERENCE 3: 105:131234

REFERENCE 4: 91:136232

L9 ANSWER 102 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **71300-96-4** REGISTRY
CN L-Leucinamide, L-isoleucyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C19 H37 Cl N6 O3
CI COM
LC STN Files: CA, CAPLUS



6 REFERENCES IN FILE CA (1967 TO DATE)
6 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 106:29204

REFERENCE 2: 103:174529

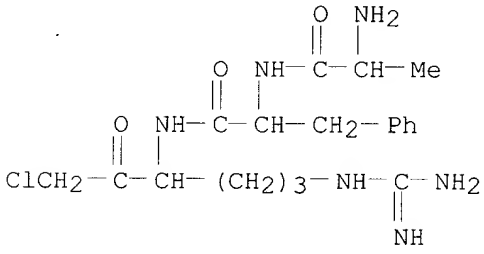
REFERENCE 3: 103:50277

REFERENCE 4: 96:30623

REFERENCE 5: 93:163452

REFERENCE 6: 91:119375

L9 ANSWER 103 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **69056-47-9** REGISTRY
CN L-Phenylalaninamide, L-alanyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C19 H29 Cl N6 O3
CI COM
LC STN Files: CA, CAPLUS, TOXLIT



8 REFERENCES IN FILE CA (1967 TO DATE)
8 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 111:208724

REFERENCE 2: 103:174529

REFERENCE 3: 100:2589

REFERENCE 4: 96:30623

REFERENCE 5: 95:182948

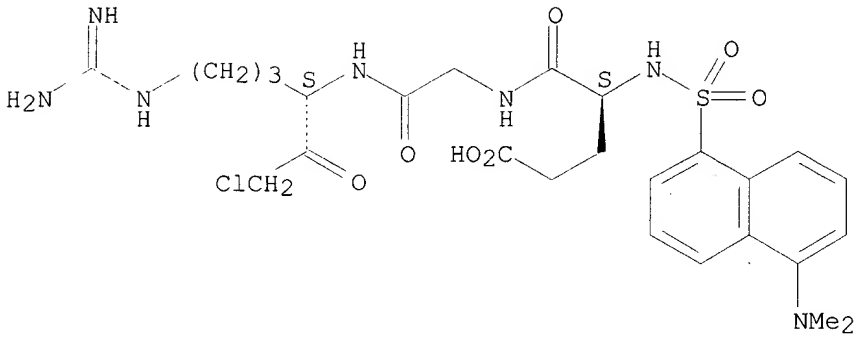
REFERENCE 6: 93:163452

REFERENCE 7: 92:175119

REFERENCE 8: 90:68372

L9 ANSWER 104 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **69024-84-6** REGISTRY
CN Glycinamide, N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-.alpha.-glutamyl-N-[(1S)-4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Glycinamide, N-[[5-(dimethylamino)-1-naphthalenyl]sulfonyl]-L-.alpha.-glutamyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)-
FS STEREOSEARCH
MF C26 H36 Cl N7 O7 S
CI COM
LC STN Files: CA, CANCERLIT, CAPLUS, MEDLINE, TOXLINE, TOXLIT, USPATFULL

Absolute stereochemistry.



35 REFERENCES IN FILE CA (1967 TO DATE)
5 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
35 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 132:18788

REFERENCE 2: 131:267054

REFERENCE 3: 131:2413

REFERENCE 4: 130:119600

REFERENCE 5: 130:7391

REFERENCE 6: 129:156938

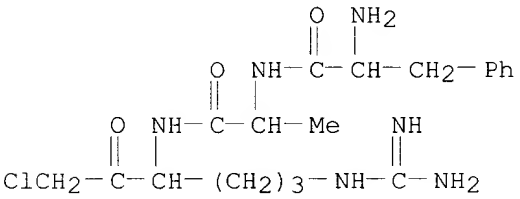
REFERENCE 7: 128:266260

REFERENCE 8: 128:136311

REFERENCE 9: 128:97711

REFERENCE 10: 125:49317

L9 ANSWER 108 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **65319-55-3** REGISTRY
CN L-Alaninamide, L-phenylalanyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C19 H29 Cl N6 O3
CI COM
LC STN Files: CA, CAPLUS, MEDLINE, TOXLIT



10 REFERENCES IN FILE CA (1967 TO DATE)
10 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 106:29204

REFERENCE 2: 103:174529

REFERENCE 3: 103:50277

REFERENCE 4: 96:176797

REFERENCE 5: 95:164392

REFERENCE 6: 93:163452

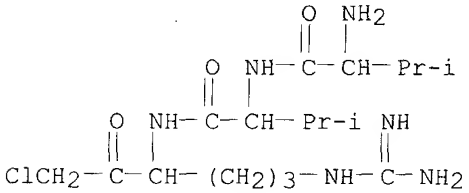
REFERENCE 7: 92:175119

REFERENCE 8: 91:119375

REFERENCE 9: 90:68372

REFERENCE 10: 88:2251

L9 ANSWER 109 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **65113-68-0** REGISTRY
CN L-Valinamide, L-valyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)
MF C17 H33 Cl N6 O3
LC STN Files: CA, CAPLUS



7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 107:132283

REFERENCE 2: 103:174529

REFERENCE 3: 96:176797

REFERENCE 4: 96:30623

REFERENCE 5: 93:163452

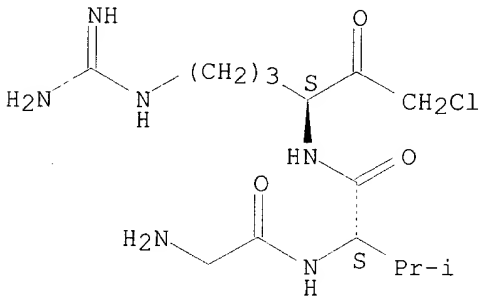
REFERENCE 6: 90:68372

REFERENCE 7: 88:2251

L9 ANSWER 111 OF 111 REGISTRY COPYRIGHT 2001 ACS
RN **63014-07-3** REGISTRY
CN L-Valinamide, glycyl-N-[4-[(aminoiminomethyl)amino]-1-(chloroacetyl)butyl]-, (S)- (9CI) (CA INDEX NAME)

OTHER NAMES:
CN Glycyl-L-valyl-L-arginylchloromethane
FS STEREOSEARCH
MF C14 H27 Cl N6 O3
CI COM
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



7 REFERENCES IN FILE CA (1967 TO DATE)
7 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 103:50277

REFERENCE 2: 96:176797

REFERENCE 3: 96:30623

REFERENCE 4: 93:163452

REFERENCE 5: 90:68372

REFERENCE 6: 88:2251

REFERENCE 7: 87:1692

=> d his

(FILE 'HOME' ENTERED AT 13:08:21 ON 06 OCT 2001)

FILE 'REGISTRY' ENTERED AT 13:08:45 ON 06 OCT 2001
L1 STR
L2 14 S L1
L3 239 S L1 FUL
SAVE TEMP L3 RUSS872FUL/A
E FACTOR IX/CN
E FIXAI
E FACTOR-IX/CN
E FACTOR-9/CN
E FACTOR 1X
E FACTOR 1X/CN
E THROMBOSIS
L4 644 S FACTOR(L)(IX? OR 1X?) OR THROMBOSIS OR CLOT? OR ANTICOAGULANT

FILE 'HCAPLUS' ENTERED AT 13:15:33 ON 06 OCT 2001

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L5          124 S L3
L6       257934 S L4 OR ?FACTOR?(5N)(IX? OR 1X?) OR ?THROMBOS? OR ?CLOT? OR ?CO
L7           51 S L5 AND L6

     FILE 'HCAPLUS' ENTERED AT 13:18:27 ON 06 OCT 2001
               SELECT HIT RN L7 1-51

     FILE 'REGISTRY' ENTERED AT 13:21:25 ON 06 OCT 2001
L8          118 S E1-E118
L9          111 S L3 AND L8

=> logoff hold
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL
                                                       ENTRY    SESSION
FULL ESTIMATED COST                                    92.79     394.55

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)          SINCE FILE      TOTAL
                                                       ENTRY    SESSION
CA SUBSCRIBER PRICE                                     0.00     -29.99

 SESSION WILL BE HELD FOR 60 MINUTES
STN INTERNATIONAL SESSION SUSPENDED AT 13:26:41 ON 06 OCT 2001
Connection closed by remote host
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